Breast cancer control in low and middle income countries

cost-effectiveness and other considerations

Sten Zelle

Colofon

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Er is alleen het leven,

het leven dat je maakt.

Het wordt steeds sneller donker,

het wordt steeds vroeger laat.

(De Dijk)

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CHAPTER 1

General introduction

Those who start at the bottom can only rise

Prologue

Breast cancer is among the most well-known and researched public health problems in the world. In the last decades, increasing numbers of women have been diagnosed with breast cancer. This has led to an extensive increase in medical interventions, mostly in high-income countries (HICs), where more resources and infrastructure are available. These medical interventions (e.g., screening, surgery, and systemic therapy) have had a positive effect on the chances of surviving breast cancer [1,2]. Currently, women who are diagnosed with breast cancer in an early stage of the disease can reasonably expect to be cured and to have a disease-free future [3]. Although a diagnosis of breast cancer in HICs is still extremely disturbing for patients and their relatives, breast cancer is no longer the death sentence it was decades ago. However, for many women living in low- and middle-income countries (LMICs), the prognosis still is very poor [1,4]. At the same time, the incidence of breast and other cancers and the costs for controlling these diseases have continued to increase in both LMICs and HICs toward disproportionately high levels [5,6]. Resource constraints are a major factor in the complex discussion on how to best control the breast cancer, which is an ongoing issue that requires continual intensive research and collective efforts on a global scale. As part of these efforts, this thesis provides information for LMICs on the breast cancer control interventions that give the greatest value for money.

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A short history of breast cancer

It is important to set forth a history of breast cancer to understand how human beings dealt with breast cancer in the past as well as how some people still perceive breast cancer in certain (remote) parts of the world. The history of breast cancer is full of attempts to understand the nature of the disease and to control it by physical removal (surgery), burning (cautery), cell destruction (chemo and radiotherapy), and therapy targeted to cell receptors (bio-modulation) [7]. It is also important to note that most medical discoveries relating to cancer control were only made in the last decades.

Some of the earliest evidence of cancer can be found among fossilized bone tumors, human mummies from ancient Egypt, and ancient manuscripts. The oldest description of breast cancer is in the Egyptian Edwin Smith Papyrus, which dates to about 1600 BC [8]. The papyrus describes eight cases of ulcers of the breast that were treated by cauterization with a tool called the "fire drill." Egyptian physicians wrote also that there was no treatment for the mysterious disease [9]. It took another 2000 years before the disease was given a name, karkinos, the Greek word for crab.

Ancient physicians and medical researchers posited several theories as to the cause of breast cancer. The "imbalance of humors" (blood, phlegm, yellow bile, and black bile) theory of Hippocrates (400 B.C.) and Galen (200 A.D.) was widely accepted for almost two millennia [10,11]. Other imagined causes included divine punishment, lack of (or too much) sexual activity, physical injuries, fear of breast cancer, and the cessation of menstruation. Only in the eighteenth century was the "black bile" of the "imbalance of humors" theory replaced with "lymph" in the understanding of breast cancer. Infectious diseases were quite common in the eighteenth century, and numerous new theories as to the cause of breast cancer were then proposed, ranging from inspissated milk, trauma, personality type, exposure to bad air, and infection [7].

In the nineteenth century, when improvements in sanitation and infectious disease control increased the lifespans of women, breast cancer became more common, and the disease then received increased attention from the medical community [12]. This led to the first successful method for treating breast cancer, surgical removal of lymph nodes, breast tissue, and chest muscle (together with the widespread usage of disinfectant and sterile gloves). While surgical removal of ulcers was proposed by Hippocrates in the Greek era (400 B.C.) and was done in the Islamic world (the tenth through twelfth centuries), surgery was considered barbaric in European Christendom (the fifth through fifteenth centuries) [7]. Around 1882, surgeon William Stewart Halsted began performing and perfecting mastectomies [4]. Halsted's mastectomies were invasive, requiring the removal of breasts, lymph nodes, and underlying muscle, and this radical procedure often left patients with long-term pain and disability.

Almost a century later, the lumpectomy was introduced in the 1970s, a much less invasive surgical procedure that removed only the cancerous tumor and the surrounding affected tissue [11]. In 1985, breast cancer patients receiving a lumpectomy followed by radiation treatment were found to have equal survival outcomes to those undergoing a more invasive mastectomy [13]. Around this time, chemotherapy also became available. Chemotherapy could also be used to shrink tumors before surgery as well as to treat metastasized cancer and prevent recurrences after surgery. Many other medical interventions were introduced during the twentieth century, including hormonal therapies, staging systems, mammography, breast reconstruction following surgery, and new diagnostic methods (e.g., magnetic resonance imaging, sentinel lymph node biopsy, frozen section) [14].

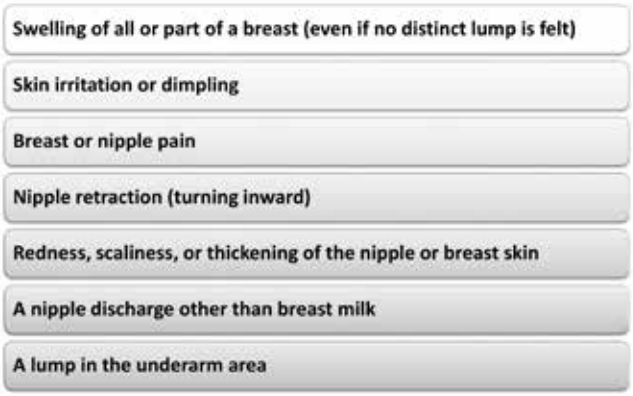
In the past three decades, scientists have experimented with combinations of treatments to improve the outcomes of breast cancer patients. This has led to a better understanding of the disease and to the development of less invasive, more targeted treatments and new options to diagnose and manage the disease (see Controlling breast bancer below). Despite these advances, however, breast cancer remains an important health problem, and one that continues to require intensive research and intense discussions on how to best control it.

Clinical manifestation and staging of breast cancer

Initially, breast cancer may not cause any symptoms. A lump may be too small for a woman to feel or to cause any noticeable changes. In some cases, the first noticeable symptom of breast cancer is a new lump or mass in the breast or thickened breast tissue that can be detected by a woman or a doctor. A lump that is painless, hard, and has uneven edges is more likely to be cancerous. However, cancers can be tender, soft, and rounded, and thus it is important for women to have anything unusual checked by a physician.

According to the American Cancer Society, any of the unusual changes in the breast shown in the figure below can be a symptom of breast cancer (Figure 1).

Figure 1. *Symptoms of breast cancer*



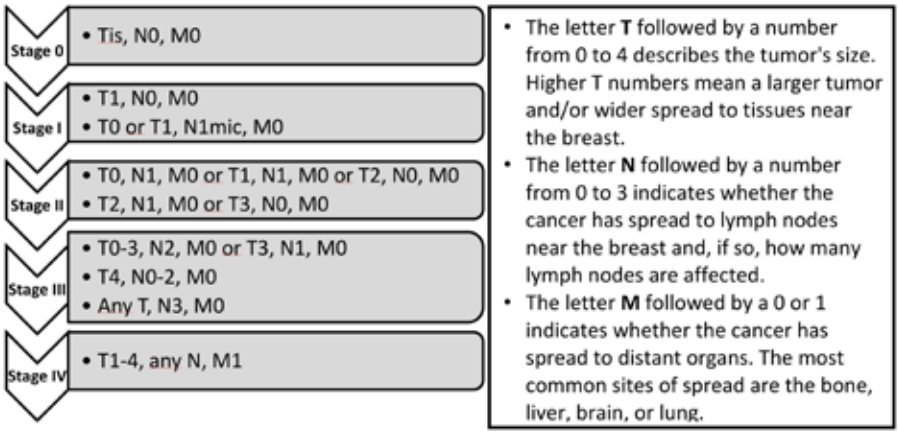
Source: the American Cancer Society [15].

However, these changes are most often related to less serious conditions that are not cancerous, such as infections or cysts. Invasive breast cancer is diagnosed in only about one in 20 women who go to their physicians with breast cancer symptoms [16,17], although this number generally depends on the level of awareness of signs and symptoms in the population.

In countries with well-established breast cancer screening programs, abnormal breast changes are often found by a screening mammogram, leading to further testing. However, up to 15% of women eligible for screening are diagnosed with a cancerous breast mass not detected by the mammogram (mammographically occult disease), and another 30% are found to have a breast mass in the interval between mammograms (interval cancers). Therefore, regardless of the availability of a breast cancer screening program, women should be generally aware of the early signs of breast cancer described above.

If breast cancer is confirmed through further testing, the extent of the cancer can be described by stage. Breast cancer staging is the process of determining how widespread the cancer is; it depends on whether the cancer is invasive or non-invasive, the size of the tumor, how many lymph nodes are involved, and whether it has spread to other parts of the body (metastasis). The staging process usually comprises physical examination, biopsy, imaging tests (clinical staging), and surgery (pathologic staging). The most commonly used system to describe the stages of breast cancer is the American Joint Committee on Cancer's (AJCC) TNM system, which classifies breast cancers into four invasive stages (stages I to IV) (Figure 2).

Figure 2. *The American Joint Committee on Cancer's (AJCC) TNM staging system*



Source: figure created by author.

Breast cancer stage is one of the most important factors in determining the prognosis of the disease and the options for treatment. It therefore plays a key role in this thesis.

Risk factors of breast cancer

The first large-scale case-control study among women with breast cancer was performed in 1923 by Janet Lane-Claypon, one of the founders of modern epidemiology [18]. The aforementioned "imbalance of humors" theory had been discarded by this time [19], and this new research identified several breast cancer risk factors relating to age at menopause, parity, age at first birth, and duration of lactation that are still considered valid today. Since this important epidemiological review, several risk factors for breast cancer have been investigated and documented (Table 1). However, for the majority of women presenting with breast cancer, it is not possible to identify specific risk factors [20,21].

Many of the documented risk factors are linked to estrogens—more specifically, to reproductive factors associated with prolonged exposure to endogenous estrogens [22]. Early menarche, late menopause, and late age at first childbirth are among the most important risk factors for breast cancer, while breastfeeding seems to have a protective effect [20,21]. Exogenous hormones, such as oral contraceptives and hormonal therapy for menopause, cause a small increase in breast cancer risk, and this risk seems to decrease once use stops [23]. A familial history of breast cancer increases the risk of breast cancer by a factor of two or three. Mutations in certain genes (particularly in BRCA1, BRCA2, and p53) greatly increase the risk of breast cancer, but these mutations are uncommon and only account for a small number of breast cancer cases.

Modifiable risk factors - that is, lifestyle factors, such as alcohol use, obesity, and physical inactivity, have also been documented for breast cancer. Danaei et al. reported that 21% of global breast cancer mortality is attributable to the joint hazard of alcohol use, overweight and obesity, and physical inactivity [24]. The percentage of attributable cancer deaths of these risk factors together differed by almost 10% between low- and middle-income countries (LMICs) and high-income countries (HICs) (18% and 27%, respectively).

The differences between LMICs and HICs in breast cancer incidence can partly be explained by dietary effects in combination with later first childbirth, lower parity, and shorter breastfeeding [25]. The increasing adoption of a western lifestyle in LMICs is an important determinant in the increase of breast cancer incidence in these countries [26].

Table 1. *Overview of breast cancer risk factors*

Risk factor type	Relative risk ≥ 4,00	Relative risk 2,00 > 4,00	Relative risk 1,25 > 2,00	Relative risk ≥ 0,80
Sex, age and residence	o Female o Increasing age (>50 years) o High income country			
Family history and genetics	o BRCA1 gene o BRCA2 gene o ATM or TP53 gene (p53) mutation carrier	o Two or more first-degree relatives with breast cancer CHEK2 mutation carriers	o One first-degree relative o multiple second-degree relatives with breast cancer	
Breast conditions	o DCIS in same breast o LCIS o High breast density	o Atypical deuctal hyperplasia	o DCIS in opposite breast o Proliferate BBD without atypia	
Reproductive and menstrual history			o Age at first period (<12 years) o Age at menopause (>55 years)	o Parity o Four births or more o Age at first birth <25 years o Breastfeeding > 12 months
Endogenous hormones		o High circulating levels of oestrogen [a]	o High circulating levels of androgens o High circulating levels of IGF-1 and IGFBP-3 [a]	
Exogenous hormones			o Use of contraceptives within past 10 years o Use of combined hormone replacement therapy	o Use of tamoxifen for more than 5 years o Use of raloxifene
Body size and lifestyle behaviors			o Height>175 cm [a] o BMI>25 kg/m2 [a] o Daily intake of 3 or more alcoholic drinks	o Obesity [b] o Physical inactivity o Smoking
Medical history or treatment	o Radiation treatment for Hodgkin's disease before age 30 years o History of breast cancer in opposite breast		o History of cancer in other organs o Treatment with high-dose ionising radiation o In utero exposure to DES	
Environmental			o High-dose ionising radiation, especially before age 20 o Light at night/shift work	

Table adapted from the National Breast and Ovarian Cancer Centre (NBOCC) and printed with their permission [27]. DCIS = Ductal carcinoma in situ; LCIS = Lobular carcinoma in situ. BBD = Benign breast disease; IGF= Insuline-like growth factor; IGFBP = Insuline-like growth factor binding protein; BMI = Body mass index; DES = diethylstilbestrol. [a] Post-menopausal breast cancer only. [b] Pre-menopausal breast cancer only.

The global burden of breast cancer

Even though risk factors for breast cancer have been identified and documented (as described in the previous section), breast cancer remains a major public health problem throughout the world. Among women, it is the most common cancer in both HICs and LMICs. It ranks second when both sexes are considered (below lung cancer) and accounts for ten percent of all new cancer diagnoses worldwide each year [28]. Although breast cancer is a very common and recognizable disease throughout the world, outcomes of breast cancer patients vary significantly between HICs and LMICs.

In 2012, an estimated 1.67 million new breast cancer cases were diagnosed worldwide, about 25% of all female cancer cases. Of all these new breast cancer cases, about 883,000 (53%) were diagnosed in LMICs, compared to 794,000 cases in HICs (47%) [29]. Breast cancer incidence rates vary about fivefold around the world and are generally higher in most HICs. However, incidence rates are increasing in countries with low rates of the disease [30]. As mentioned in the previous section, this can partly be explained by dietary effects in combination with later first childbirth, lower parity, shorter breastfeeding, and the adoption of a western lifestyle [25]. Studies of migrants from low-risk to high-risk countries show that incidence rates increase and eventually become similar to those among the rest of the population in the new country [23].

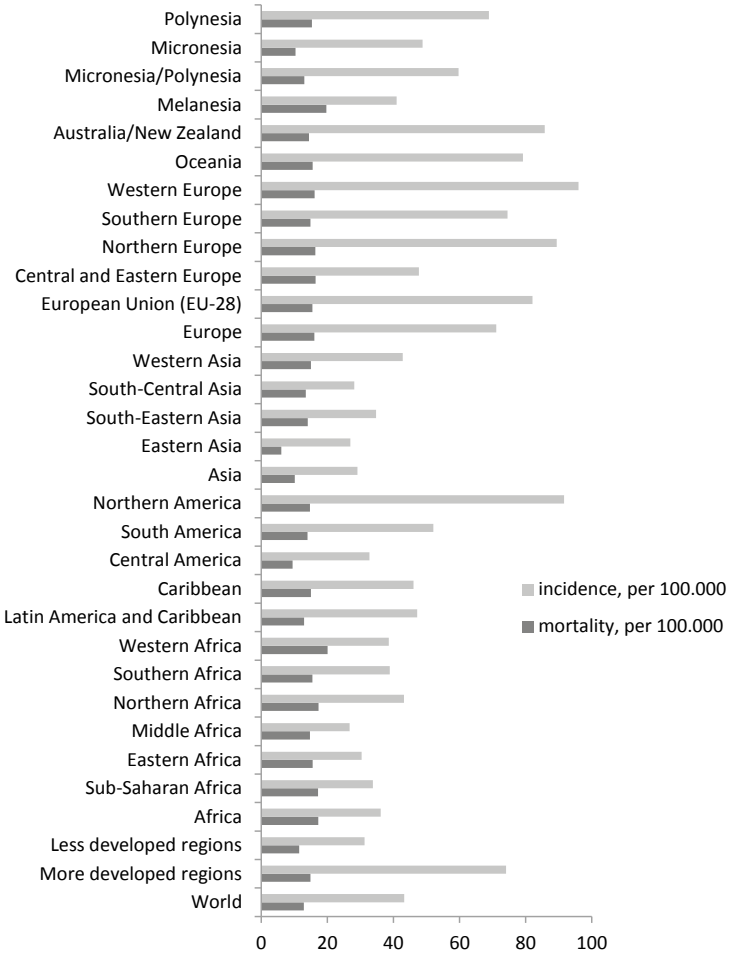
Breast cancer is also one of the most common causes of death from cancer among women globally. With 522,000 deaths in 2012, the disease ranks as the fifth-leading cause of death from cancer overall. Most women diagnosed with breast cancer in HICs can reasonably expect to be cured and enjoy a long life expectancy. Such progress has been made possible by screening programs that enable early detection and by the use of multiple modality treatments [29]. However, in LMICs, under-resourced and underperforming health services continually fail to deliver adequate screening and treatments, leading to poor outcomes for patients with breast cancer[31]. This seems to be confirmed by the 2012 mortality numbers: with 324,000 deaths, breast cancer was still the most frequent cause of cancer death in women in LMICs (62%), but it was the second-leading cause of cancer death in HICs (198,000 deaths, 38%) [29].

The global differences in mortality rates, from 6 per 100,000 in Eastern Asia to 20 per 100,000 in Western Africa, are less marked than the differences in the incidence rates (see Figure 3) [29]. This is because of the more favorable survival rates for breast cancer in high-incidence countries (lower mortality-to-incidence ratios). The mortality-to-incidence ratio of breast cancer, which indicates breast cancer survival or case fatality, has a worldwide average of 31.1%. However, the differences in the ratios between HICs and LMICs are enormous; in the United States and in Africa, these rates are 18.9% and 49.0%, respectively. The bulk of the high mortality-to-incidence ratios in LMICs can be explained by the high proportion of women presenting with breast cancer in late stages. Late-stage breast cancer has a poor prognosis and outcome even in HICs.

About 16.6 million Disability Adjusted Life Years (DALYs) were lost because of breast cancer worldwide in 2011 [32]. When considering DALYs lost, breast cancer ranks fifth compared to all other cancers and accounts for about 7.5% of all DALYs lost because of cancer. About 55% of the global breast cancer burden is currently experienced in HICs. The European region accounts for 25.2% of all breast cancer DALYs lost worldwide, whereas the African and Eastern Mediterranean regions account for 9.6% and 8.1%, respectively [32]. Although much of the breast cancer burden is still experienced in HICs, breast cancer is the top cancer in women worldwide.

In spite of the numbers provided above and the improved prognosis of breast cancer in the last decades, the initial diagnosis of breast cancer is still perceived by many patients as a life-threatening event, and more than 35% of these patients experience anxiety and depression[33]. Breast cancer and cancer in general can be equally—if not more—distressing for patients' relatives, greatly affecting their daily functioning and their economic situation.

Figure 3. *Incidence and mortality rates in different world regions (2012, age standardized)*



Source: GLOBOCAN [29].

Controlling breast cancer

The previous section explained that the burden of breast cancer is increasing, particularly in LMICs. In these countries, relatively more breast cancer cases are fatal (higher mortality-to-incidence ratios) because most of these cases are diagnosed in late stages [22]. Effective and straightforward options for controlling the disease are available and could mitigate much of the breast cancer burden in these countries.
Although some risk reduction might be achieved through controlling breast cancer risk factors, these preventive strategies cannot eliminate the majority of breast cancers and breast cancer burden throughout the world. A wide range of non-preventive interventions for breast cancer control exist, particularly in HICs, ranging from mammography screening to expensive monoclonal antibody therapy (with trastuzumab) for palliation. In LMICs, where breast cancer incidence is relatively low and the majority of women are diagnosed in late stages, health systems are generally weak, and these countries often have to opt for less advanced breast control strategies.

The aim of breast cancer control is to reduce the incidence and mortality of the disease as well as to improve the quality of life with breast cancer [33]. A comprehensive breast cancer control program involves prevention, early detection, diagnosis and treatment, rehabilitation, and palliative care, and should be equitable and make the best use of available resources [22]. Comprehensive breast cancer control involves all of the above-mentioned control components. An overview of non-preventive interventions is provided in Table 2, and the most important control components are discussed in the following.

Prevention

Prevention aims at eliminating or reducing the exposure to breast cancer risk factors and could eventually have an impact in reducing the incidence of breast and other cancers in the long term. Preventive control strategies include the promotion of a healthy diet, physical activity, and the control of alcohol intake, overweight, and obesity. Some women who are at higher breast cancer risk (often genetic) prefer to remove their breasts as a preventive action. As mentioned, lifestyle choices may not be sufficient to eliminate the majority of breast cancers in the world. Future preventive strategies may improve this and could involve genetic testing to individualize patient treatment or techniques to repair or replace harmful genes before breast cancer occurs.

Table 2. Interventions along the continuum of care to control breast cancer (prevention excluded)

Control component	Sub-component	Intervention options	purpose
Early detection	Breast health awareness (education ± self-examination)	o Outreach o Basic awareness raising media campaign (BAR) o Mass awareness raising media campaign (MAR)	Early diagnosis through recognition of early signs and symptoms in symptomatic populations
	Opportunistic screening / Population-based screening	o CBE combined with usual diagnostic test o CBE combined with FNA o Analogue mammography o Digital mammography o Three-dimensional mammography o MRI* o Ultrasound* o Full field ultrasound* o Tactile imaging* o VOC breath tests* o Tomosynthesis* o Breast Computerized Tomography* o Multistatic Array Processing for Radiowave Image Acquisition*	Use of a screening test in a presumably asymptomatic population, to identify individuals with an abnormality suggestive of cancer
Diagnosis	Clinical diagnosis	o History o Physical examination o CBE o Surgical biopsy o FNA o Core needle biopsy o Imaged-guided sampling o Preoperative needle localization under mammographic or ultrasound guidance o Stereotactic biopsy o Sentinel node biopsy	Identify and classify the patient's condition or disorder allowing medical decisions on treatment and prognosis. It should help in selecting the most appropriate therapy
	Pathology diagnosis	o Cytology/pathology report o ER/PR status o Margin status o Her-2/neu status o IHC staining	
	Lab/radiologic diagnosis	o Ultrasound o Mammogram o Chest radiography o Liver ultrasound o Renal status o CBC o Bone scan o MRI o PET scan	

Control component	Sub-component	Intervention options	purpose
Treatment	Surgery	o Total mastectomy o Modified radical mastectomy o Breast conserving therapy (lumpectomy) o Sentinel node biopsy o Reconstructive surgery	Improve the survival, recurrence rates or quality of life of breast cancer patients
	Radiotherapy	o Post-mastectomy irradiation of the chest wall and regional nodes o Breast-conserving whole-breast irradiation	
	Chemotherapy	o Classical CMF o Anthracycline monotherapy or in combination o Taxanes o Capecitabine o Growth factors o Vinorelbine o Gemcitabine o Carboplatin	
	Hormonal and other therapy	o Selective ER Modifiers (tamoxifen) o Aromatase inhibitors o Swith therapy o Trastuzumab o Fulvestrant	
Follow-up and rehabilitation		o Imaging o Fysiotherapy o Physical examination	Regularly monitor if the cancer might return. Help the person regain control over the many aspects of their lives as independent and productive as possible
Palliative	Pain treatment, inpatient based or home based care	o Non-opioid and opioid analgesics o Bisphosphonates o Anti emulsives o Anti depressants o Boost radiotherapy o Emotional support o Inpatient based care o Home based care	Relief of suffering. Improve quality of life of patients and relatives

*Source: Table created by author. CBE = Clinical breast examination; FNA = Fine needle aspiration; MRI = Magnetic resonance imaging; VOC = Volatile organic compounds; ER = Estrogen receptors; PR = Progesterone receptors; IHC = Immunohistochemical; CBC = Complete blood count; PET = positron emission tomography; CMF = Cyclophosphamide Methotrexate Fluorouracil. *These techniques could, for example, complement mammography in a screening program, or could be used as standalone screening techniques; however, they are still controversial.*

Early detection

Early detection aims at finding breast cancer in an earlier stage when treatment is more effective. The early detection component of breast cancer control programs can comprise a breast health awareness sub-component to raise awareness of the early signs and symptoms of breast cancer in symptomatic populations. This may lead to the earlier recognition of breast cancer signs and symptoms so that women will seek care and have an earlier diagnosis (this is also called "early diagnosis"). However, most early detection components include the screening of asymptomatic populations (also called "secondary prevention"). Screening was first proposed in the 1950s [34], and it remains the cornerstone of breast cancer control for improving breast cancer outcomes and survival[22].

Mammography screening is widely used for early detection in HICs and is generally applied to women between 50 and 70 years of age. The exact benefits and harms of mammography screening are still under discussion, but according to the latest discussions, the impact of mammography screening on breast cancer mortality in HICs is about 20% to 30% [35–37]. The harms of screening include undergoing an uncomfortable or painful test, experiencing anxiety, and undergoing biopsies from false positive test results. However, the most debated harm of breast cancer screening is over-diagnosis (i.e., the detection of harmless tumors that would never have been detected in the absence of screening).

Discussions on the kind of screening test and the population that should be targeted for screening are complex. LMICs could, for example, base screening strategies on mammography, clinical breast examination (CBE), ultrasound, tactile imaging, or breath tests [38, 39]. Thus far, however, the impact and practicability of these screening tests are largely unknown in LIMCs because of a lack of cancer registries and experimental studies [39–42]. In addition, the impact of screening and the population that should be targeted for screening in LMICs also depend on diversity in epidemiology, socio-cultural aspects, and the organization of health care. Moreover, the available budget for breast cancer control is often limited in LMICs.

Diagnosis, treatment, and palliative care

Irrespective of the early detection intervention used, continuity and quality of actions across the entire continuum of care (diagnosis, treatment, follow-up) are essential for a well-functioning control program. After the detection of a breast abnormality, the next important determinant of an effective control program is the diagnostic process, which is a combination of careful assessment and investigations determined by three sub-components: clinical diagnosis, pathology tests, and diagnosis by laboratory and imaging tests. Various techniques exist throughout these three sub-components; they are presented in Table 2. Nevertheless, at the basic level, a clinical exam and biopsy (open or FNA), a cytological report of the biopsy (size, grade, TNM, stage), a diagnostic imaging test (mammogram or ultrasound), and an ER/PR test are required to select an effective treatment strategy [43].

A wide range of treatment options exist for breast cancer patients. Treatment can be divided into three sub-components: surgery, radiation, and systemic treatment (chemotherapy and hormonal therapy). Basic-level therapies involve the removal of the tumor and lymph nodes (lumpectomy or modified mastectomy), chest wall and regional lymph node irradiation, AC (doxorubicin and cyclophosphamide) or CMF chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and tamoxifen for those eligible [43]. The choice of the treatment schedule and its effectiveness vastly depend on the number of axillary lymph nodes involved, the tumor size, histological grade, hormonal receptor status, and the age and preferences of the patient [44]. In addition, treatment approaches should include psychosocial support and rehabilitation. Therapy schedules including taxanes, trastuzumab, aromatase inhibitors, or bisphosphonates are expensive, and could require much of the available resources in LMICs [43].

Palliative care is an approach that improves the quality of life of patients and their relatives facing problems with life-threatening diseases. It can prevent or relieve suffering through early identification and careful assessment and treatment of pain and physical, social, and spiritual suffering [22,33]. Palliative care can be provided by inpatient care, home-based care, or a combination of the two. Breast cancer patients with metastatic disease or with recurrent breast cancer are generally incurable. Depending on the localization of the metastases, mastectomy, hormonal therapy, chemotherapy, bisphosphonates, or a combination can be used. Most patients also benefit from non-opioid and opioid analgesics (morphine) and radiotherapy (boost). In most of the world, the majority of breast cancer patients present with advanced disease. For them, the only realistic treatment option is pain relief and palliative care. Effective approaches to palliative care are available and should be considered for implementation. This is particularly important for LMICs, in which most breast cancer patients are diagnosed in advanced stages of the disease.

With better control of infectious diseases and improvements in living conditions and health care, life expectancy has increased worldwide. However, at the same time, the number of cancers and other non-communicable diseases has increased significantly [45], with breast cancer as the most prevalent female cancer. Much is currently known about the causes of breast cancer and effective means by which to control the disease. The establishment of national breast cancer control strategies could facilitate controlling the disease in LMICs even if their resources are severely limited [33].

The economic burden of breast cancer

In the previous sections, the health burden of breast cancer and options for controlling the disease were presented. However, breast cancer not only represents a large health burden, but also a significant economic burden to societies. Substantial healthcare costs are associated with the early detection, diagnosis, and management of the disease. Moreover, some patients are unable to continue working, and many rely on friends and family for support during treatment or in the last phases of the disease.

The economic burden of breast cancer is not well documented, and comprehensive estimates on the cost of breast cancer are limited. A study by Luengo-Fernandez et al. estimated the economic burden of cancer across the 27 EU countries in 2009, as well as the specific proportions of the total cost attributable to breast, colorectal, lung, and prostate cancers [46]. Across the EU population, the healthcare costs of all cancers were equivalent to €102 per citizen in 2009. Lung cancer had the highest total economic cost (€18.8 billion, 15% of overall cancer costs), followed by breast cancer (€15.0 billion, 12%). When the total economic costs for breast cancer (€15.0 billion) are broken down into their various cost components, healthcare costs account for 45% of the total costs for breast cancer (€6.7 billion), productivity losses account for 34% (€5.0 billion), and informal care accounts for 21% (€3.2 billion) of the total costs for breast cancer. Most interesting is that drugs were the largest component of breast cancer healthcare costs (€3.1 billion, 46% of healthcare costs). Moreover, the healthcare costs per EU member (per capita) varied greatly for breast cancer, ranging between €2 (Malta) and €2,342 (Germany).

The global economic costs of breast cancer were estimated in another study (the Economist Intelligence Unit) and were reported in 2009 [47]. Although the estimates in this report cannot be compared with the study of Luengo-Fernandez et al. and are less detailed, the estimated global economic costs for breast cancer were US$28.4 billion. The healthcare costs accounted for 46% ($13.1 billion) of the total costs, and the non-direct healthcare costs ($7.6 billion) and productivity losses ($7.7 billion) each account for 27% of the total breast cancer costs. One striking feature of the estimated US$28.4 billion breast cancer costs is that 96% of these global costs were spent by HICs. This seems disproportionate since only 15% of the world's population lives in HICs [47].

The global economic burden of breast cancer seems substantial in terms of both medical and non-medical costs. The medical health care costs attributable to breast cancer vary greatly between countries, reflecting differences in total health care spending. Non-medical costs, however, seem generally higher (account for more or less 55% of all costs) than medical costs. This is possibly because of the reproductive age of breast cancer patients: many cases occur in women below 65 years, especially in LMICs. These breast cancer cases correspond to relatively high productivity losses of ill-health and seeking and undergoing care.

Breast cancer consumes resources at an astonishing rate and, while high-income countries account for 96% of total spending on breast cancer, the impact of the disease is felt around the world [47]. However, studies on the economic burden of breast cancer that consider both healthcare and non-healthcare costs are sparse. Such studies are important because they can complement studies on the health burden and support decisions on efficient resource allocation for breast cancer control.

Health economics and cost-effectiveness analysis (CEA) for breast cancer control

Given the impact of breast cancer on healthcare costs and the financial constraints faced by most LMICs, identifying breast cancer control interventions that can significantly reduce the burden of the disease at low costs is extremely important. The scientific discipline of health economics connects health with the resources consumed in promoting it. The underlying problem with health economics is that people have nearly infinite healthcare needs, but there are finite (limited) resources with which to satisfy them. Therefore, choices have to be made about which healthcare needs are most important and how best to use the available resources. The field of health economics attempts to illuminate these choices [48].

A principal analytic tool that is often used within the field of health economics is cost-effectiveness analysis (CEA). This method is used to compare different health interventions by assessing the gains in health relative to the costs of each intervention. CEA supports decision making by identifying the areas of action in which the greatest health gains can be achieved within the available budget.

The basic calculation in CEAs involves dividing the cost of an intervention in monetary units (e.g., US dollars, Euros, or local currencies) by the expected health gain measured in natural units (e.g., number of life-years, Disability Adjusted Life Years (DALYs), or Quality Adjusted Life Years (QALYs). The result is summarized in the cost-effectiveness ratio (CER) of the intervention and the incremental cost-effectiveness ratio (ICER) of the intervention (relative to another intervention). For example, assume that a certain breast cancer medicine costs $120 dollars per patient for the entire regimen. Because of this medicine, the patient is able to live three years longer. This corresponds to a CER of $40 dollars per life-year saved ($40 dollars per LYS). Assume that another regimen costs $300 dollars and that patients taking the medicines in this regimen generally live six years longer. The CER of this more expensive regimen is then $50 dollars per life-year saved ($50 dollars per LYS).

$$\text{CER: } \frac{\text{costs of intervention A (\$120)}}{\text{health effects of intervention A (3 years)}} = \$40/\text{LYS}$$

$$\text{CER: } \frac{\text{costs of intervention B (\$300)}}{\text{health effects of intervention B (6 years)}} = \$50/\text{LYS}$$

$$\text{ICER: } \frac{\Delta \text{ costs of A-B (\$180)}}{\Delta \text{ health effects of A-B (3 years)}} = \$60/\text{extra LYS}$$

However, in this case, the incremental cost-effectiveness ratio (ICER), which is defined as the ratio of the change in the costs of intervention B (compared to alternative A) to the change in the effects of intervention B (compared to alternative A) is $60 additional dollars per life-year saved ($60 per LYS). The ICER should be used to compare the differences between the costs and health outcomes of the two alternative interventions since they compete for the same resources.

These ratios correspond to a pure form of utilitarianism, the concept of maximizing health value for the available money. Hence, CEAs provide the clearest and simplest way to promote value for money in health and allow comparisons throughout the health sector. To use CERs and ICERs to choose what to buy, decision makers must determine a maximum willingness to pay for units of health gain (e.g., the World Bank has described health interventions that cost less than $100 dollars per life-year saved as highly cost-effective for poor countries) unless other criteria are considered to justify buying something with relatively poor cost-effectiveness. The calculations of the CERs and ICERs by themselves do not monetize the intrinsic value of health [49].

Various health economic studies on breast cancer screening, genetic testing, drug treatments, and follow-up have been conducted and reviewed [50–56]. Prior health economic studies typically report the costs and effects of an intervention given an existing level of control in a specific country and are aimed at a specific group of breast cancer patients. For example, many of the CEAs have focused on comparing different strategies (e.g., comparing age ranges, screening tests, and screening frequencies) for screening in HICs [56]. Costs per life-year saved range from $2,450 to $14,790 in Europe, and from $28,600 to $47,900 in the United States [49]. This indicates that the cost-effectiveness of breast cancer interventions varies greatly by country and depends on many factors, including disease epidemiology, health care systems, costs, and compliance rates. Moreover, the majority of studies have been conducted in HICs and cannot be directly translated to low-resource settings.

Thesis rationale and objective

The sustainability of health care systems and the need to prioritize efficient health investments are at the top of many national political agendas. Economic evaluations generate essential information to support decisions on alternative health policy options. Data on the cost-effectiveness of a particular control strategy are very powerful in showing how much health benefit can be obtained for a given investment relative to other possible strategies.

Current information on the cost-effectiveness of breast cancer control interventions for LMICs is very limited because most cost-effectiveness studies in this area have been conducted in HICs. Considering the differences in incidence rates, age at diagnosis, and constrained resources compared to Western populations, LMICs require different solutions than the more conventional strategies to control breast cancer. Breast cancer control interventions that appear to be cost-effective in HICs may not be cost-effective in LMICs even when the lower cost of providing health services is taken into account. Therefore, it is necessary to identify breast cancer control interventions in LMICs that are effective and efficient in averting deaths and improving quality of life at low costs.

The aim of this thesis is: To provide evidence-based information on the value for money of breast cancer control interventions in LMICs, to guide LMICs in planning or improving their national breast cancer control programs.

Thus, the specific research question of this thesis is: ***What is the cost-effectiveness of a range of breast cancer control interventions along the continuum of care in a number of LMICs?***

To comprehensibly guide LMICs in improving breast cancer control, this thesis also focuses on other considerations next to cost-effectiveness.

Unfortunately, it is not possible to include all low- and middle- income countries within the scope of this thesis. The LMICs for which cost-effectiveness estimates for breast cancer control were assessed in this thesis are Ghana, Mexico, Costa-Rica, India, and Peru. These countries were selected on the basis of the national importance of breast cancer control as expressed by the Ministries of Health of these countries in addition to the interest in cost-effectiveness in these countries.

To understand the approach used throughout this thesis, it is important to first discuss the general WHO-CHOICE approach applied and the mathematical model developed to analyze the general cost-effectiveness of various breast cancer control interventions.

Approach used in this thesis

WHO-CHOICE approach

To allow for meaningful comparisons across different LMICs, the generalized cost-effectiveness (GCEA) analysis approach proposed by WHO-CHOICE is used in this thesis [57]. WHO-CHOICE is a program of the World Health Organization that helps countries set priorities with consideration for impact and cost-effectiveness [58]. The WHO-CHOICE tools involve disease models and costing tools, which are preset with regional average data (default settings). For a GCEA in a specific country, data for epidemiology, intervention impacts, and prices can easily be replaced with data that are more appropriate for the country in question.

The WHO-CHOICE methodology proposes the evaluation of all interventions that may be considered policy-relevant, either because they are highly cost-effective or highly cost-ineffective. All interventions, including those that are independent and those that are mutually exclusive, are compared to a common comparator, which is a situation in which the impacts of currently implemented interventions are removed. It is commonly designated as the "counterfactual null." This counterfactual null represents a more comparable reference across populations than the current intervention (or mix of interventions) used in standard cost-effectiveness analysis. This approach enables the comparison of interventions across diseases and populations.

In economic analyses, the costs and benefits are recorded and assessed from a certain perspective. The choice of this perspective must be derived logically from the research question posited by the country under investigation. WHO-CHOICE usually considers an extensive healthcare perspective and generally does not include non-health costs. In addition to the cost of interventions as determined from best practice guidelines, this perspective includes the costs of administration, training, and program elements [57].

In addition, to interpret CERs and ICERs for choosing what to purchase and what not to, decision makers must determine a set of cost-effectiveness thresholds (different willingness to pay levels for units of health). WHO-CHOICE denotes an intervention as "cost-effective" if it produces a healthy year of life for less than three times the gross domestic product (GDP) per capita. If an intervention produces a healthy year of life for less than the GDP per capita, it is denoted as "very cost-effective" [57]. As mentioned before, calculation of the CERs and ICERs by itself does not monetize the intrinsic value of health. The maximum willingness to pay per unit of health should be determined by local decision makers, and the proposed WHO-CHOICE thresholds are rules of thumb that should not be interpreted overly strictly.

Using the WHO-CHOICE methodology, the impact of a certain intervention on the population health of a specific population of interest gives the estimate of effectiveness. This effectiveness is applied to a population level model (a tool called PopMod) to project the likely impact in Disability Adjusted Life Year (DALYs) over a period of 100 years.

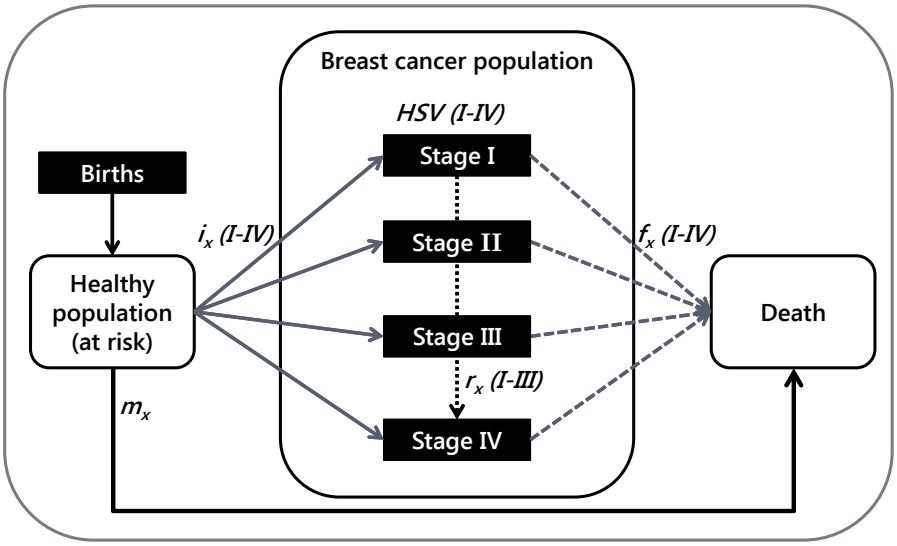
It is of critical importance that the different intervention scenarios are described accurately using all essential information to interpret the estimated costs and benefits. This includes the strict definition of the treatment pathway for clinical interventions as well as which procedures are incorporated and which are not. However, studying different interventions in the field of breast cancer immediately reveals a vast number of early detection, diagnosis, and treatment options (see Table 2). In recent decades, the diagnosis and treatment of breast cancer has become increasingly complex with specified diagnoses and tailored treatment combined with surgery, radiotherapy, chemotherapy, and hormonal therapy regimens. Although the aim of WHO-CHOICE is to include all interventions of interest, it would be impossible to include all possible single and mutually exclusive breast cancer intervention scenarios. Therefore, in this thesis, intervention scenarios are incorporated that consider AJCC stages I, II, III, and IV [59] and conform to the most common clinical practice guidelines established in LMICs [43]. Although this is much less specific than the approaches described in many diagnostic guidelines or common practices, it offers the possibility of using population-level data. Moreover, it is in line with the aim of this thesis - to evaluate the cost-effectiveness of breast cancer control strategies to support national-level decisions.

Overview of the mathematical modeling approach

Figure 4 represents a simplified sketch of the model used to estimate the cost-effectiveness of breast cancer interventions. As can be seen in this figure, the population modeled includes three categories: the healthy, the sick, and the dead. The healthy population (or population at risk) in this model is equivalent to the total number of women without breast cancer in the country under study. The sick population consists of the number of prevalent and incident breast cancer cases, and this category is divided into the four AJCC breast cancer stages (stages I to IV). Each AJCC stage in this category has a corresponding health state valuation (HSV, or disability weight) and case fatality rate.

The estimated effectiveness of interventions is expressed in terms of changes in case fatality rates (treatment interventions), health state valuations (treatment interventions), or stage distribution (awareness raising and screening interventions). Interventions are implemented for a period of ten years, after which the epidemiological rates return to their counterfactual level in the null scenario. As such, modeling a specific intervention involves using evidence-based, country-specific data to address the intervention's impact on these factors.

Figure 4. *Applied breast cancer model*



Graphical representation of the model showing the relationships between the different health states through the incidence rates of breast cancer (i_x I-IV), the different stage specific case fatality rates (f_x I-IV), and the background mortality (m_x). Stage specific relapse rates (r_x I-III), to stage IV were used to correct the disability weights (HSV I-IV).

Thesis outline

The overarching goal of this thesis is to provide evidence-based information for LMICs on the breast cancer control interventions that give the greatest value for money. The provision of this information will be presented through various scientific studies over eight chapters (Chapters Two to Nine).

In ***chapter two***, a systematic review is presented on previous economic analyses of breast cancer control in LMICs. As previously mentioned, the international literature on the costs and health effects of breast cancer control focuses mainly on HICs, and there is little information on the cost and effectiveness of breast cancer interventions in LMICs. This systematic review provides an overview of what economic information from LMICs is currently available and discusses the relevant considerations for future economic analyses.

Chapter three discusses the development of a simple model to predict the stage distribution of different breast cancer screening alternatives in diverse populations. With the scarcity of studies on screening methods in LMICs, it seems difficult to estimate the effectiveness of breast cancer screening in LMICs. The developed model can assist in estimating the impact of CBE screening and mammography screening in LMICs.

In ***chapter four to seven*** a number of case studies are presented that provide the costs, effects and cost-effectiveness of different breast cancer control options in five individual LMICs (Ghana, Peru, Mexico, Costa-Rica, and India). The results of these case studies could possibly be used for the development or improvement of national breast cancer control strategies in these countries.

In ***chapter eight***, the cost-effectiveness of different cancer control interventions for cervical, colorectal, and breast cancer in two different world sub-regions (Southeast Asia and Sub-Saharan Africa) are presented. This can guide resource allocation decisions in LMICs with relatively similar resources and overall mortality. The study provides general insights into the comparative cost-effectiveness of control strategies across and beyond individual cancers.

This thesis also focuses on other considerations than just cost-effectiveness, as cost-effectiveness is only one of the multiple criteria relevant to priority setting. In ***chapter nine***, a multi-criteria decision analysis (MCDA) method specifically for breast cancer control is discussed. If we want policy makers to make good use of the results from CEAs, other criteria should be considered and assessed simultaneously. MCDA is also able to account for all the important considerations relating to equity, feasibility, budget, health level, and responsiveness. This last study therefore presents the development of a simple MCDA rating tool, which can be used in the priority-setting process. This tool may improve the consideration of multiple relevant criteria, including CEA results, to support comprehensive breast cancer control strategies in LMICs.

Chapter ten concludes the thesis. In this chapter, the contributions and limitations of this thesis are discussed. A number of important next steps in the field of global breast cancer control and recommendations for future research are proposed in this chapter.

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I

CHAPTER 2

Economic analyses of breast cancer control in low- and middle-income countries

a systematic review

A good place to start is where you are now

Sten G Zelle, Rob M Baltussen

Systematic Reviews 2013;2:20

Abstract

Background

To support the development of global strategies against breast cancer, this study reviews available economic evidence on breast cancer control in low- and middle-income countries (LMICs).

Methods

A systematic article search was conducted through electronic scientific databases, and studies were included only if they concerned breast cancer, used original data, and originated from LMICs. Independent assessment of inclusion criteria yielded 24 studies that evaluated different kinds of screening, diagnostic, and therapeutic interventions in various age and risk groups. Studies were synthesized and appraised through the use of a checklist, designed for evaluating economic analyses.

Results

The majority of these studies were of poor quality, particularly in examining costs. Studies demonstrated the economic attractiveness of breast cancer screening strategies, and of novel treatment and diagnostic interventions.

Conclusions

This review shows that the evidence base to guide strategies for breast cancer control in LMICs is limited and of poor quality. The limited evidence base suggests that screening strategies may be economically attractive in LMICs – yet there is very little evidence to provide specific recommendations on screening by mammography versus clinical breast examination, the frequency of screening, or the target population. These results demonstrate the need for more economic analyses that are of better quality, cover a comprehensive set of interventions and result in clear policy recommendations.

Keywords

Breast cancer control, economic evaluation, systematic review, low- and middle-income countries, cost-effectiveness, noncommunicable diseases.

Background

Noncommunicable diseases (NCDs) have become increasingly important in low- and middle-income countries (LMICs). Once considered a problem only in high-income countries (HICs), more and more patients who suffer from cancers and other NCDs are now observed in LMICs [1]. This is mainly due to the ageing populations and changing lifestyles in LMICs [2]. The global importance of NCDs has recently been acknowledged through the UN Summit on NCDs, held by the UN General Assembly in September 2011. As highlighted in the summit, the most prominent cause of cancer death among women in LMICs is breast cancer, accounting for 269,000 deaths (12.7% of all cancer deaths) in 2008 [3,4].

In HICs, many efforts have been undertaken to control breast cancer, leading to various improvements in breast cancer outcomes [5,6]. Strategies for breast cancer control are geared towards early detection and early treatment, and although its benefits are still open to discussion [7-9], mammography screening has been widely implemented [10-12]. In these countries, the selection of breast cancer control strategies has often been guided by economic analyses, demonstrating the value of alternative interventions [13-16].

In contrast to the established breast cancer control strategies in HICs, breast cancer is often neglected in LMICs and control strategies lack evidence-based information [17-20]. Policy-makers in LMICs cannot adopt similar breast cancer control strategies as implemented in HICs because most LMICs rely on much smaller budgets, and both the costs and effectiveness of control strategies are highly dependent on the population characteristics and the functioning of the health system [11,20,21].

Against this background, the present review provides an inventory of economic analyses of breast cancer control in LMICs. The paper's objectives are to present the available economic evidence from LMICs and to assess the methodological quality of the analyses. This research could improve the evidence base on cost-effective breast cancer interventions and could strengthen breast cancer control policy in LMICs.

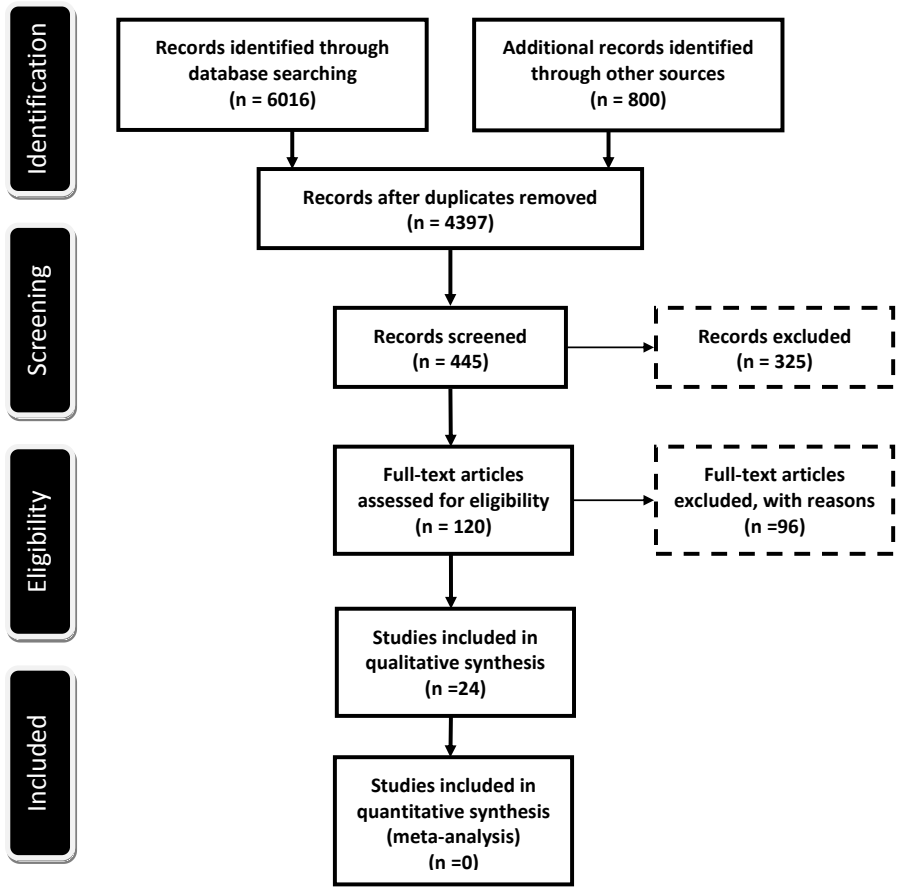
Methods

Search strategy and selection criteria

In this review, we analyzed publications from the MEDLINE index using PubMed, the Web of Science, Scopus, and Google Scholar. We searched the literature using the keyword 'breast cancer', combined with the keywords: 'developing countries', 'Asia', 'USSR', 'Middle-East', 'Eastern Europe', 'West-Indies', 'China', 'Russia', 'India', 'Africa', or 'limited resource', or combined with: 'cost-benefit', 'cost-effectiveness', 'costing', or 'cost analysis'. Additionally, we searched these indexes using 'breast neoplasms', 'developing countries,' and 'economics' in MeSH terms. Our search took place in January 2013, and was limited to publications in English. Studies were included only if they concerned breast cancer and originated from LMICs as listed by The World Bank [22].

The selection process is shown in Figure 1. In step 1, articles found by our search in the various indexes were merged in a database, which was then corrected for duplications (in Google Scholar, because of the large number of articles founds, we screened titles until the point that we did not find any further relevant title among the last 500 screened titles; in total, we screened 800 titles in this database). In step 2 we screened the titles of these articles, in step 3 the abstracts and in step 4 the remaining articles were read completely. We excluded publications for which no full-text article versions were available, or those not published in English. Furthermore, we excluded articles that only mentioned costs or cost-effectiveness without presenting original data.

Figure 1. *Selection process of analyzed publications*



Study characteristics

We documented the following characteristics from the reviewed articles: country or region, base year of cost data, study population, and breast cancer stage(s) considered. The stage was categorized as stage I to IV according to the American Joint Committee on Cancer [23].

We documented the following methodological characteristics: type of economic evaluation –cost analysis or cost of illness analysis, separately reported costs and effects, cost-effectiveness analysis, cost–benefit analysis, and cost–utility analysis; study design – experimental, observational (cohort, case control, or cross-sectional), model based, and other designs; study perspective – non-healthcare perspective (for example, productivity loss, travel costs, co-payments), healthcare perspective (for example, hospital administration costs, treatment costs), and societal perspective including non-healthcare and healthcare costs; time horizon; and outcome measure for effectiveness (disability-adjusted life years, quality-adjusted life years, life years saved, lives saved, and intermediate outcome measures).

The following qualitative characteristics were documented: sources for estimation of effectiveness, sources for estimation of resource utilization, discount rates used, sensitivity analysis for assumptions, and reported incremental analysis. We classified sources for estimation of effectiveness and resource utilization by primary data collection (for example, patients, questionnaires), secondary data collection (for example, records), literature based, expert opinion, and other. We also noted whether discount rates were used on costs, effects, both costs and effects, or not at all.

We also registered the study objective, the evaluated interventions, and the main study conclusions for each reviewed article.

Study evaluation

We used an established checklist by Drummond and Jefferson to judge the quality of the economic evaluations [24,25]. A three-point response scale was added, similar to Gerard and colleagues [25], to more specifically grade the quality of each item on the checklist. Scores on this scale ranged from 0 (not considered), to 1 (partially considered) to 2 (fully considered). A few adjustments to the checklist by Drummond and Jefferson were necessary to create a more responsive scoring system for our particular set of economic studies. We removed those items that were not applicable to any of the reviewed studies (for example, on productivity changes), and combined some items that were otherwise putting too much emphasis to certain domains in the overall score (for example, on health state valuations and discount rates). The adapted checklist is provided in Table 1. We summed up all scores, and compared this with the maximum attainable score to calculate the mean quality score of a study (as a percentage of the maximum attainable score). We accounted for items that were not relevant to the study under scrutiny (for example, studies that studied costs and effects in a single year were not criticized for not applying any discount rate in the analyses).

Two reviewers (SGZ and RMB) evaluated each publication for conformance with this checklist, and consensus was reached when scores differed. We followed PRISMA guidelines for reporting this systematic review.

Table 1. *Checklist for quality of economic evaluations*

Item	Fully	Partial	Not at all	Not appropriate
Original checklist	2 points	1 point	0 points	NA
Study design				
1. The research question is stated				
2. The economic importance of the research question is stated				
3. The viewpoint(s) of the analysis are clearly stated and justified (relating to a particular decision-making context)				
4. The rationale(s) for choosing the alternative programs or interventions which are compared is stated				
5. The alternatives being compared are clearly described				
6. All relevant alternatives are included				
7. The choice of economic evaluation is justified in relation to the questions addressed				
Effectiveness estimation				
8. The primary outcome measure for the economic evaluation is clearly stated				
9. The source(s) of effectiveness estimates used is clearly stated				
10. Details of the design and results of the effectiveness study are given (if based on a single study)				
11. Details of the methods of synthesis or meta-analysis of estimates are given (if based on multiple studies)				
12. Data and methods used to value health states and other benefits are stated and justified.				
Cost estimation				
14. Indirect non-healthcare costs are included or discussed				
15. Quantities of resources are reported separately from their unit costs				
16. Methods for the estimation of quantities and unit costs are described and justified.				
17. Details of currency of price adjustments for inflation or currency conversion are given				

Item	Fully	Partial	Not at all	Not appropriate
Original checklist	2 points	1 point	0 points	NA
Analysis				
18. Time horizon of costs and benefits are stated				
18. Details of any model used are given				
19. The choice of model used and the key parameters on which it is based are justified				
20. The discount rate(s) is stated				
21. The choice of rate(s) is justified				
22. Details of statistical tests and confidence intervals are given for stochastic data				
23. Sensitivity analysis is performed:				
2) Probabilistic (bootstrap/Monte Carlo)				
1) Deterministic (one way /multiple way)				
24. The choice of variables in sensitivity analysis and the range over which these variables are varied is justified				
25. Incremental analysis is performed and reported				
Interpretation of results				
26. Major outcomes are presented in a disaggregated as well as aggregated form				
27. The answer to the study question is given				
28. Relevant alternatives are compared				
29. Conclusions follow from the data reported				
30. Conclusions are accompanied by the appropriate caveats such as generalizability, equity, feasibility, and implementation				

This checklist was adapted from Drummond and Jefferson [24].

Results

Search results

The stepwise selection of articles by our selection criteria is presented in Figure 1. Our search strategy resulted in a total of 6,816 studies: 679 studies from PubMed, 328 studies from Web of Science, 5,009 studies from Scopus, and 800 from Google Scholar, respectively. In step 1, by merging the results of all individual search strategies and excluding duplication, the total number of hits was reduced to almost 4,400. Upon screening of titles (step 2), abstracts (step 3) and full texts (step 4), we eventually identified 24 articles that met our inclusion criteria.

Study characteristics

Table 2 describes the baseline characteristics of the 24 included studies. We found eight studies from Asia, most concerning China, India and Iran. Five studies were on a global or sub-regional level, while there were five studies from Africa, three from Europe and three from Latin America. A total of 10 studies evaluated breast cancer screening in combination with treatment (n = 10), assessing mammography screening (n = 9), clinical breast examination (CBE) (n = 3), magnetic resonance imaging (n = 1), ultrasound (n = 1), biopsy (n = 1), elasticity imaging (n = 1), and tactile imaging (n = 1), respectively [26-36]. These studies evaluated a variety of age groups and screening frequencies (Table 2). One study reported on a mass-media intervention to improve the early detection of breast cancer in Ghana [35]. Seven studies evaluated only treatment interventions including drug therapy (n = 4), oophorectomy (n = 1), radiotherapy (n = 1), and treatment in general (n = 1) [37-42]. Other studies examined the costs of diagnostic interventions (n = 3) or did not consider a specific intervention (n = 2) [43-48].

Table 2. *Characteristics of reviewed studies, ordered by base year of cost data*

Authors	Region / country	Base year of cost data	Study population	Breast cancer stage considered	Economic evaluation type	Study design	Perspective	Time horizon	Effectiveness outcome measure	Sources for estimation of effectiveness	Sources for estimation of resource utilization	Discount rates used	Sensitivity analysis for assumptions presented	Incremental analysis reported
Groot and colleagues, 2006 [28]	World sub-regions	2000	Female population at risk, in AfrE, AmroA, SearD	All	Cost-effectiveness analysis	Model based	Healthcare	100 years	DALYs	Literature based	Secondary data collection	On both costs and effects	Yes	Yes
Okonkwo and colleagues, 2008 [30]	India	2001	Female population at risk	All	Cost-effectiveness analysis	Model based	Healthcare	25 years	Life years saved	Secondary data collection	Secondary data collection	On both costs and effects	Yes	Yes
Munshi, 2009 [41]	Worldwide	Varying from 2002 to 2007	Breast cancer patients in general	All	Report on costs and effects separately	Other	Healthcare	NA	Intermediate outcome measures	Literature based	Literature	NA	NA	NA
Sarvazyan and colleagues, 2008 [32]	Worldwide	Varying from 2003 to 2007	Female population at risk	All	Cost-effectiveness analysis	Other	Not stated	1 year	Life years saved	Literature based	Literature	NA	Yes	No
Fonseca and colleagues, 2009 [38]	Brazil	2005	Hypothetical cohort of 64-year-old postmenopausal women	All	Cost-effectiveness analysis	Model based	Healthcare	Lifetime	Life years saved	Literature based	Expert opinion	On both costs and effects	Yes	Yes
Ginsberg and colleagues, 2012 [27]	Sub-Saharan Africa and South East Asia	2005	Female population at risk, in SearD and AfrE	All	Cost-effectiveness analysis	Model based	Healthcare	100 years	DALYs	Literature based	Secondary data collection	On both costs and effects	Yes	Yes
Salomon and colleagues, 2012 [31]	Mexico	2005	Female population at risk	All	Cost-effectiveness analysis	Model based	Healthcare	100 years	DALYs	Literature based	Secondary data collection	On both costs and effects	Yes	Yes
Pakseresht and colleagues, 2011 [48]	India	2006/2007	103 women with primary breast cancer in a tertiary hospital	All	Cost analysis/ cost of illness	Observational	Non-healthcare	2 years	NA	NA	Primary data collection	NA	NA	NA

Authors	Region / country	Base year of cost data	Study population	Breast cancer stage considered	Economic evaluation type	Study design	Perspective	Time horizon	Effectiveness outcome measure	Sources for estimation of effectiveness	Sources for estimation of resource utilization	Discount rates used	Sensitivity analysis for assumptions presented	Incremental analysis reported
Yazihan and Yilmaz, 2006 [34]	Turkey	2007	Female population at risk	All	Cost-effectiveness analysis	Other	Healthcare	6 years	DALYs	Secondary data collection	Secondary data collection	None	No	No
Bastani and Kiadaliri, 2012 [49]	Iran	2008	Patients younger than 75 with node-positive breast cancer	All	Cost-utility analysis	Experimental	Healthcare	8 months	QALYs	Primary data collection	Primary data collection	NA	No	NA
Liubao and colleagues, 2009 [39]	China	2008	Model cohort of 1,000 51-year-old operable breast cancer patients	All	Cost-effectiveness analysis	Model based	Healthcare	Lifetime	QALYs	Secondary data collection	Secondary data collection	On both costs and effects	Yes	Yes
Astim, 2011 [36]	Turkey	2010	Female population at risk older than 30	All	Report on costs and effects separately	Model based	Healthcare	10 years	Intermediate outcome measures	Secondary data collection	Literature	Yes	No	No
Zelle and colleagues, 2012 [35]	Ghana	2010	Female population at risk	All	Cost-effectiveness analysis	Model based	Healthcare	100 years	DALYs	Literature based	Primary data collection	On both costs and effects	Yes	Yes
Bai and colleagues, 2012 [42]	China	2012	Model cohort of women aged 51.7, with early stage breast cancer after lumpectomy	I and 2	Cost-effectiveness analysis	Model based	Healthcare	Lifetime	QALYs	Literature based	Literature/expert opinion	On both costs and effects	Yes	Yes
Arredondo and colleagues, 1995 [43]	Brazil	Not clear	Hypothetical breast cancer case	All	Cost analysis/ cost of illness	Observational	Healthcare	NA	NA	NA	Expert opinion	NA	No	No
Boutayeb and colleagues, 2010 [37]	Morocco	Not clear	Early-stage breast cancer patients in Morocco	Not clear	Cost-effectiveness analysis	Observational	Healthcare	1 year	Life years saved	Literature based	Secondary data collection	NA	No	No

Authors	Region / country	Base year of cost data	Study population	Breast cancer stage considered	Economic evaluation type	Study design	Perspective	Time horizon	Effectiveness outcome measure	Sources for estimation of effectiveness	Sources for estimation of resource utilization	Discount rates used	Sensitivity analysis for assumptions presented	Incremental analysis reported
Denewer and colleagues, 2010 [26]	Egypt	Not clear	Female population at risk between 25 and 65 years	All	Report on costs and effects separately	Experimental	Healthcare	2 years	Intermediate outcome measures	Primary data collection	Not clear	None	No	No
Guggisberg and colleagues, 2011 [46]	Cameroon	Not clear	Women who underwent FNA in a rural hospital	All	Report on costs and effects separately	Observational	Healthcare	5 weeks	Intermediate outcome measures	Primary data collection	Not clear	NA	No	No
Kobayashi, 1988 [44]	Worldwide	Not clear	NA	NA	Cost analysis/ cost of illness	Observational	Healthcare	NA	Intermediate outcome measures	Primary data collection	Primary data collection	NA	NA	NA
Love and colleagues, 2002 [40]	Vietnam and China	Not clear	Premenopausal Vietnamese and Chinese breast cancer patients, considered for surgery	2	Cost-effectiveness analysis	Experimental	Healthcare	15 years	Life years saved	Primary data collection	Not clear	On both costs and effects	No	Yes
Mousavi and colleagues, 2008 [29]	Iran	Not clear	Female population at risk between 35 and 69	All	Report on costs and effects separately	Other	Healthcare	1 year	Life years saved	Expert opinion	Expert opinion	NA	No	No
Nasrinossadat and colleagues, 2011 [47]	Iran	Not clear	51 patients that underwent surgical excision of nonpalpable breast masses	All	Report on costs and effects separately	Observational	Healthcare	3 to 4 years	Intermediate outcome measures	Primary data collection	Not clear	None	No	No
Thomas and colleagues, 1999 [45]	Nigeria	Not clear	Patients who received FNA between 1994 and 1997	All	Report on costs and effects separately	Observational	Patient	NA	Intermediate outcome measures	Primary data collection	Not clear	NA	NA	NA

DALYs = disability-adjusted life years; FNA = fine needle aspiration; NA = not applicable; QALY = quality-adjusted life year.

The methodological study characteristics of the reviewed studies are presented in Table 2. The base year of cost data in the included studies was generally not from before year 2000, and could not be identified in eight studies. The majority of studies combined both costs and effects in a single cost-effectiveness estimate (n = 13), and the majority of these were based on mathematical models (n = 9). Most studies used a healthcare perspective (n = 19), and only one study included non-healthcare costs [48]. Studies used a time horizon varying between 5 weeks and the lifetime of the study population. Most reviewed studies used intermediate outcome measures (that is, clinical effects n = 8), life years saved (n = 6), or disability-adjusted life years (n = 5) as their main effectiveness outcome, while quality-adjusted life years were less frequently used (n = 3).

Study quality

Table 2 summarizes the quality of the included studies, as indicated by the percentage score. The quality of all studies ranges from 23 to 86%. Studies by Ginsberg and colleagues, Zelle and colleagues, and Bai and colleagues had the highest total average scores, and these were all modeling studies [27,35,42].

Studies generally scored poorly on the domain 'estimation of costs', at an average 34% of the maximum obtainable score across all studies. The average score for 'study design' was 73%, while the quality of the domains 'estimation of effectiveness', 'analysis', and 'interpretation of results' was scores as 70%, 51%, and 68%, respectively.

Study findings

As described earlier, most studies evaluated breast cancer screening in combination with treatment. Studies in Mexico, Poland, Turkey identified mammography screening as a cost-effective intervention [31,33,34,36], whereas studies in India, Ghana and Egypt found other strategies (such as CBE screening or mass-media awareness raising) to be economically more attractive (Table 3) [26,30,35]. Sarvazyan and colleagues proposed another breast cancer screening option: tactile imaging as an alternative to several other interventions [32].

Table 3. *Interventions compared, study objectives, and main study conclusions of reviewed articles*

Authors	Interventions compared	Study objective	Conclusions by authors
Groot and colleagues, 2006 [28]	Combinations of individual stage I to IV treatment and an extensive mammography screening control program	To assess the cost-effectiveness of breast cancer control that covers various interventions in different settings	Stage I treatment and an extensive screening control program are the most cost-effective interventions
Okonkwo and colleagues, 2008 [30]	Mammography screening, CBE screening among different age groups and in different frequencies	To assess which screening program should be implemented in India	CBE screening in India compares favorably with mammography screening in developed countries
Munshi, 2009 [41]	Several treatment interventions	To present pragmatic cost-saving breast cancer interventions	Intelligent use of knowledge about the disease can help us to exploit new techniques for maximum therapeutic gain with minimal investment
Sarvazyan and colleagues, 2008 [32]	CBE, mammography, ultrasound, magnetic resonance imaging, biopsy, elasticity imaging, tactile imaging	To review the diagnostic accuracy, procedure cost, and cost-effectiveness of currently available techniques for breast screening and diagnosis.	Tactile imaging has the potential to provide cost-effective breast cancer screening and diagnosis
Fonseca and colleagues, 2009 [38]	Anastrozole vs. tamoxifen in the adjuvant setting of early breast cancer	To determine cost-effectiveness of anastrozole, compared with tamoxifen, in the adjuvant treatment of early stage breast cancer in Brazil	Anastrozole is more cost-effective than tamoxifen in the adjuvant setting of early breast cancer
Ginsberg and colleagues, 2012 [27]	Stage 1 to 4 treatment individual, treatment of all stages, biennial mammography screening 50 to 70 vs. null scenario	To determine the cost-effectiveness of 81 interventions to combat breast, cervical and colorectal cancer at different geographic coverage levels, to guide resource allocation decisions in LMICs	For breast cancer, although expensive, mammography screening in combination with treatment of all stages is cost-effective in both regions (I$2,248 to 4,596/DALY). Treating early-stage breast cancer is more cost-effective than treating late-stage disease
Salomon and colleagues, 2012 [31]	Stage 1 to 4 treatment individual, treatment of all stages, screening (annual CBE >25 years + mammography annual >50 years + mammography biennial >40 to 49 years) vs. null scenario	Analyze the cost-effectiveness of 101 intervention strategies directed at nine major clusters of NCDs in Mexico (including breast cancer), to inform decision-makers	Treatment of all stages is cost-effective and treatment of early stages is more cost-effective than late stage treatment. Nationwide screening has an incremental CEA of I$22,000/DALY and is potentially cost-effective
Pakseresht and colleagues, 2011 [48]	NA	To estimate the expenditure audit of women with breast cancer in a tertiary hospital in Delhi	Expenditure on treatment for breast cancer depends on many factors, including the size and stage of the cancer, the woman's age, use of private hospitals and insurance
Szynglarewicz and Matkowski, 2011 [33]	Polish screening program costs vs. other countries	To show preliminary results of the Polish screening program	Population-based mammographic screening conforming the European quality standards is cost-effective even for middle-income countries
Yazihan and Yilmaz, 2006 [34]	Mammography screening in age group 50 to 69 vs. treatment only	To determine the efficiency of resource usage in mammography screenings and the impact on breast cancer stages in Turkey	Mammography screening is economically attractive for Turkey

Authors	Interventions compared	Study objective	Conclusions by authors
Bastani and Kiadaliri, 2012 [49]	Docetaxel, doxorubicin and cyclophosphamide (TAC) vs. 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) in node-positive breast cancer patients	To evaluate the cost-utility of TAC and FAC in node-positive breast cancer patients	FAC was a dominant option versus TAC in the short term. In this study, TAC resulted in higher costs and lower QALYs over the study period
Liubao and colleagues, 2009 [39]	AC (doxorubicin/cyclophosphamide) vs. TC (docetaxel/cyclophosphamide)	To estimate the cost-effectiveness of AC (doxorubicin/cyclophosphamide) vs. TC (docetaxel/cyclophosphamide)	TC appears to be more effective and more costly than AC. TC may be viewed as cost-effective using the general WHO threshold
Astim, 2011 [36]	Annual and biennial mammography screening in various age groups (40+, 45+, 50+, 55+, 60+ years) vs. no screening	To evaluate the cost-effectiveness, optimal minimum age and screening interval for a screening program in Turkey	Results of the simulation suggests that women over 40 in Turkey should be screened by mammography biennially
Zelle and colleagues, 2012 [35]	Treatment interventions, biennial mammography and CBE screening interventions, awareness raising interventions, palliative care interventions vs. null scenario	To analyze the cost, effects and cost-effectiveness of breast cancer control interventions in Ghana, and identify the optimal mix of interventions to maximize population health	Both screening by clinical breast examination and mass media awareness raising seem economically attractive interventions ($1,299 and $1,364/DALY). Mammography screening is not cost-effective
Bai and colleagues, 2012 [42]	Radiotherapy vs. no radiotherapy after surgery	To assess the cost-effectiveness of additional radiotherapy for women with early breast cancer after breast-conserving surgery	In health resource-limited settings, the addition of radiotherapy is a very cost-effective strategy (–$420/QALY) in comparison with no-radio therapy in women with early breast cancer
Arredondo and colleagues, 1995 [43]	Case management costs for infrastructure, human resources, laboratory, hospital stay, drugs, mastectomy, disposable material, curing material	To develop a system for monitoring costs of case management for each disease (breast cancer, cardiac calve disease and enteritis and bronchopneumonia)	Economic analyses hold important information for decision-making
Boutayeb and colleagues, 2010 [37]	Three chemotherapy regimes, AC, AC + taxanes, AC + taxanes + trastuzumab	To evaluate the total cost of chemotherapy in early stage breast cancer	Moroccan health authorities need to devote between US$13.3 to 28.6 million to treat women by chemotherapy every year
Denewer and colleagues, 2010 [26]	CBE-based screening with selective mammography vs. no screening	To evaluate the disease pattern of screen-detected cancers and determine the effectiveness of CBE-based screening	CBE-based screening with selective mammography is feasible, effective and improves the results of breast cancer management in Egypt
Guggisberg and colleagues, 2011 [46]	On-site FNA clinic vs. shipping of specimens	To assess the feasibility of an on-site cytopathology clinic in a rural hospital in Cameroon	Cytopathology (FNA) is a reliable alternative for tissue diagnosis in low-resource settings
Kobayashi, 1988 [44]	Costs and performance of breast echography in different institutions	To analyze the economics and cost performance of breast echography in various institutions	The best cost performance, internationally, can be achieved by mechanical and real-time electronic linear scanners

Authors	Interventions compared	Study objective	Conclusions by authors
Love and colleagues, 2002 [40]	Adjuvant oophorectomy and tamoxifen vs. oophorectomy and tamoxifen for recurrence after observation.		
	To evaluate costs, disease-free and overall survival after surgical oophorectomy and tamoxifen in premenopausal Vietnamese women with operable breast cancer	Vietnamese and Chinese women with hormone receptor-positive operable breast cancer benefit from adjuvant treatment with surgical oophorectomy and tamoxifen	
Mousavi and colleagues, 2008 [29]	Mammography screening in age groups 35 to 69 and 50 to 69 and no screening	To decide whether mammography screening should be established in Iran or whether other options are needed	Benefits of other policies than mammography screening need to be explored
Nasrinossadat and colleagues, 2011 [47]	Methylene blue dye injections vs. wire localization	To report experience in marking nonpalpable breast masses by injection of methylene dye	Marking with methylene blue dye is a simple, effective and low-cost method for localization of nonpalpable breast masses
Thomas and colleagues, 1999 [45]	FNA cytology vs. surgical tissue biopsy	To assess the results and limitations of a Nigerian FNA clinic	FNA cytology can help improve the management and cost of care of patients with palpable masses

CEA = cost-effectiveness analysis; CBE = clinical breast examination; DALY = disability-adjusted life year; FNA = fine needle aspiration; LMIC = low- and middle-income country; NCD = noncommunicable disease; QALY = quality-adjusted life year; WHO = World Health Organization.

Table 4. *Summary of quality assessment and domain scores of reviewed studies*

Authors		Scored domains					Summary scores		
		Study design	Effectiveness estimation	Cost estimation	Analysis	Interpretation of results	Number of items scored	Sum of scores	Total average score
Groot and colleagues, 2006 [28]	Score granted	12	7	6	16	9	29	50	1.72
	% of maximum (domain) score	86%	88%	75%	89%	90%			86
Okonkwo and colleagues, 2008 [30]	Score granted	12	6	3	16	10	28	47	1.68
	% of maximum (domain) score	86%	100%	38%	100%	100%			84%
Munshi, 2009 [41]	Score granted	7	7	0	1	4	21	19	0.90
	% of maximum (domain) score	50%	70%	0%	50%	40%			45%
Sarvazyan and colleagues, 2008 [32]	Score granted	7	7	0	1	4	21	19	0.90
	% of maximum (domain) score	50%	70%	0%	50%	40%			45%

Authors		Scored domains					Summary scores		
		Study design	Effectiveness estimation	Cost estimation	Analysis	Interpretation of results	Number of items scored	Sum of scores	Total average score
Fonseca and colleagues, 2009 [38]	Score granted	14	6	1	13	10	28	44	1.57
	% of maximum (domain) score	100%	100%	13%	72%	100%			79%
Ginsberg and colleagues, 2012 [27]	Score granted	12	8	8	18	10	29	52	1.79
	% of maximum (domain) score	86%	100%	75%	89%	100%			90%
Salomon and colleagues, 2012 [31]	Score granted	12	6	5	14	8	29	45	1.55
	% of maximum (domain) score	86%	75%	63%	78%	80%			78%
Pakseresht and colleagues, 2011 [48]	Score granted	7	1	4	3	5	15	20	1.33
	% of maximum (domain) score	88%	50%	50%	75%	63%			67%
Szynglarewicz and Matkowski, 2011 [33]	Score granted	5	3	2	1	5	24	15	0.625
	% of maximum (domain) score	88%	50%	50%	75%	63%			33%
Yazihan and Yilmaz, 2006 [34]	Score granted	12	0	3	2	5	28	22	0.79
	% of maximum (domain) score	86%	0%	38%	13%	50%			40%
Bastani and Kiadaliri, 2012 [49]	Score granted	13	8	4	7	8	25	40	1.6
	% of maximum (domain) score	93%	100%	50%	70%	80%			80%
Liubao and colleagues, 2009 [39]	Score granted	13	7	4	16	10	29	50	1.72
	% of maximum (domain) score	93%	88%	50%	89%	100%			86%
Astim, 2011 [36]	Score granted	9	5	3	8	7	28	32	1.14
	% of maximum (domain) score	64%	63%	38%	50%	70%			57%
Zelle and colleagues, 2012 [35]	Score granted	14	7	7	14	10	29	52	1.79
	% of maximum (domain) score	100%	88%	88%	78%	100%			90%
Bai and colleagues, 2012 [42]	Score granted	13	8	5	18	8	29	52	1.79
	% of maximum (domain) score	93%	100%	63%	100%	80%			90%

Authors		Scored domains					Summary scores		
		Study design	Effectiveness estimation	Cost estimation	Analysis	Interpretation of results	Number of items scored	Sum of scores	Total average score
Arredondo and colleagues, 1995 [43]	Score granted	10	NA	1	0	7	18	18	1.00
	% of maximum (domain) score	71%	NA	13%	0%	70%			50%
Boutayeb and colleagues, 2010 [37]	Score granted	12	4	4	1	6	25	27	1.08
	% of maximum (domain) score	86%	50%	50%	13%	60%			54%
Denewer and colleagues, 2010 [26]	Score granted	10	4	0	2	5	25	21	0.84
	% of maximum (domain) score	71%	50%	0%	20%	50%			42%
Guggisberg and colleagues, 2011 [46]	Score granted	3	6	2	1	5	25	24	0.96
	% of maximum (domain) score	21%	75%	25%	13%	50%			35%
Kobayashi, 1988 [44]	Score granted	4	4	1	NA	3	19	12	0.63
	% of maximum (domain) score	29%	67%	13%	NA	30%			32%
Love and colleagues, 2002 [40]	Score granted	9	6	1	10	8	27	34	1.26
	% of maximum (domain) score	64%	100%	13%	63%	80%			63%
Mousavi and colleagues, 2008 [29]	Score granted	5	1	0	1	3	22	10	0.45
	% of maximum (domain) score	36%	25%	0%	13%	30%			23%
Nasrinossadat and colleagues, 2011 [47]	Score granted	75	5	0	0	5	25	17	0.68
	% of maximum (domain) score	50%	63%	0%	0%	50%			34%
Thomas and colleagues, 1999 [45]	Score granted	7	4	0	0	6	21	17	0.81
	% of maximum (domain) score	50%	67%	0%	0%	60%			41%
Total average domain score (%)	73%	73%	70%	34%	51%	68%			

If items were not applicable (NA) for a reviewed paper, the maximum obtainable (domain) score was reduced with 2 points per item.

Studies evaluating treatment interventions typically favored the novel interventions. Anastrozole was more cost-effective than tamoxifen in a Brazilian study [38], oophorectomy and tamoxifen after recurrence was shown to be favorable in Vietnamese and Chinese patients [40], additional radiotherapy after breast-conserving surgery was very cost-effective in China [42], and chemotherapy consisting of a docetaxel and cyclophosphamide regimen was more attractive compared with an doxorubicin and cyclophosphamide regimen also in Chinese patients [39]. There was only one study with a negative suggestion for the novel and more costly intervention docetaxel, doxorubicin, cyclophosphamide, as compared with the more conventional 5-fluorouracil, doxorubicin, dyclophosphamide regime [49].

Studies that only assessed costs and did not include effectiveness estimates, reported on costs of breast cancer for patient management in Brazil (US$1,646 per patient) [43], and the costs of patient expenditure (US$242 per patient) in India [48].
The three studies evaluating diagnostic interventions demonstrated the economic attractiveness of inexpensive interventions; that is, fine-needle aspiration cytology and methylene blue dye injections [45-47]. These interventions could be especially relevant for diagnosing breast cancer in rural settings and settings with low resources.

Discussion

This study shows that there is limited economic evidence on breast cancer control in LMICs. Only 24 economic evaluation studies were found in this review, and their quality was generally poor. Furthermore, the study populations were very diverse, as most studies examined different kinds of screening and therapeutic interventions in various age and risk groups. Owing to this poor availability, quality, and comparability, we conclude that the economic evidence base to guide strategies for breast cancer in LMICs is currently insufficient.

Our review raises a few discussion points. First, there is mixed evidence on the economic attractiveness of mammography screening. Studies in Mexico, Poland and Turkey demonstrate the intervention to be cost-effective, whereas studies in India, Ghana, and Egypt suggests that other forms of screening – for example, by CBE – provide more value for money. The evidence base is too small to generalize these findings to other LMICs, and to draw general conclusions. Also, most of the studies evaluating therapeutic interventions seem to favor the more novel – and often more expensive – therapy. These findings may be explained by many reasons, including the higher effectiveness of the novel interventions but possibly also the association between funding sources and pro-industry conclusions [50].

Second, in general, we found that the quality of the reviewed articles was poor. The majority of studies failed to score at least 50% on every domain ('study design', 'estimation of effectiveness', 'estimation of costs', 'analysis', and 'interpretation of results'). These domain scores further show that most emphasis was given to the design of the studies and the interpretation of results, whereas costs, in particular, were poorly evaluated. This calls for better adherence of studies to methodological standards for economic analyses, or the development of such standards specifically for breast cancer research. Future studies could be improved by using a checklist, and through transparent reporting of the items in checklists [25,51].

Third, the current evidence base leaves many LMICs with the difficult task of extrapolating results from other countries. The transferability of economic evaluations across countries is complicated, as clinical practice patterns, healthcare systems, and cultural and ethical practices differ across countries [52,53]. Standardized ways of adopting economic evaluations, with the help of available checklists and guidelines [24,25,51,54-58], may improve this lack of transferability. Alternatively, modeling studies could play an important role in extrapolating results from one context to another. Modeling studies, however, rely on the availability of costing and effectiveness data, and this emphasizes the need for more primary data collection on these aspects in LMICs. With data from such studies, researchers would not have to continue to rely on sensitivity analyses or extrapolating cost estimates from data in HICs. National cancer registries, mortality databases, hospital registries, and accessible publications would be essential for providing such information [59].

Fourth, and closely related, we generally advocate the use of modeling studies in the economic analysis of breast cancer control in LMICs. In addition to their use in the extrapolation of study findings, they generally appeared to be of high quality, are sufficiently flexible to include important methodological characteristics such as adequate time horizon, and seem also appropriate to evaluate a broad array of interventions across different groups.

Fifth, the most adopted type of economic evaluation was cost-effectiveness analysis, using a healthcare perspective and life years saved as the primary outcome. Although cost-effectiveness analyses using a healthcare perspective contribute very important information, productivity losses for patients suffering from breast cancer – and most probably other NCDs – can be substantial [60,61]. So far, there is no methodological consensus on estimating productivity loss and the cost of illness can vary greatly between different costing approaches (for example, human capital approach vs. friction cost approach) and also between gender, age and the type of job of patients [62]. Further research should account for economic and social characteristics of the population under study, and should try to investigate productivity losses. Additionally, life years saved may be a less appropriate outcome when palliative or preventive interventions are investigated, and the use of disability-adjusted or quality-adjusted life years may be more appropriate.

Sixth, there is currently very little economic evidence on less established interventions such as tactile imaging, awareness raising, CBE screening, or preventive and palliative interventions. Economic studies, especially in LMICs, should aim to evaluate these interventions more often (and thereby including broad target populations) and they have the potential to be economically attractive [26,30,32,35].

Finally, guidance in decision-making and recommendations for implementation are generally underemphasized in economic evaluations. By reflecting on the health system characteristics of the particular country and considering them in implementation recommendations, economic evaluations could improve their use in breast cancer policy development.

Our study has a number of limitations. Primarily, the number of articles reviewed is very limited, possibly the result of our search strategy. Besides a possible publication bias – studies with negative outcomes are less likely to be published – we searched only for articles published in English. This may explain the relatively small number of articles found, for instance, from Spanish-speaking regions or from countries where there is less emphasis on publishing research (for example, in Africa). Also, the studies included in our review vastly differed with regard to their methodology, objectives, characteristics, and study populations and hence are difficult to compare. In addition, our quality assessment of the reviewed articles was based on a checklist that gives highest scores to a full reporting of all domains. However, short reports in the form of, for example, editorials may not include all these details but may nevertheless be valid for the goals they serve. Hence, the scores for these studies should be interpreted with caution.

Conclusions

To conclude, our findings indicate that research on the costs and cost effectiveness of breast cancer control in LMICs is still in its infancy. The limited evidence base suggests that screening strategies may be economically attractiveness in LMICs – yet there is very little evidence to provide specific recommendation (on screening by mammography vs. CBE, the frequency of screening, or the target population). These results demonstrate the need for more economic analysis that are uniform, of better quality, cover a comprehensive set of interventions and result in clear policy recommendations.

Abbreviations

CBE, clinical breast examination; HIC, high-income country; LMIC, low- and middle-income country; NCD, noncommunicable disease.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
SGZ performed the search strategy, designed the inclusion criteria, reviewed all papers included in the review, developed the evaluation strategy and drafted the manuscript. RMB participated in the design of the study, the selection of relevant articles, the evaluation and classification of articles and contributed to the writing of the manuscript. Both authors reviewed and critically assessed the papers included in this review.

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2

CHAPTER 3

Predicting the stage shift as a result of breast cancer screening in low- and middle-income countries

a proof of concept

To work from nature is to improvise

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Abstract

Objective

To provide proof of concept for a simple model to estimate the stage shift as a result of breast cancer screening in low- and middle-income countries (LMICs). The amount of stage shift is an essential early detection indicator and an important proxy for the performance of screening programmes and their possible further impact. Our model could help LIMCs to decide on which control strategies to implement.

Methods

We assessed the concept of our model in three steps. First, we calculated the proportional performance rates (i.e. index number Z) based on 16 screening rounds of the Nijmegen Screening Program (384,884 screened women). Second, we used linear regression to assess the association between Z and the amount of stage shift observed in the Nijmegen Screening Program. Third, we hypothesized how Z could be used to estimate the stage shift as a result of breast cancer screening in LMICs.

Results

Our results show that stage shifts can be estimated by the proportional performance rates (Zs) using linear regression. The Zs, calculated for each screening round, are highly associated with the observed stage shifts in the Nijmegen Screening Program (Pearson's R: 0.798, R square: 0.637).

Conclusions

This study confirms that our model can predict the stage shifts in the Nijmegen Screening Program, and provides proof of concept that the model could theoretically be applied to other settings with different characteristics. This is a promising and important step, although our model should not be straightforwardly used to estimate the impact on mortality and further research should investigate the extrapolation of our model to other settings. As the amount of stage shift is an essential screening performance indicator, our model could provide important information on the performance of breast cancer screening programmes that LMICs consider implementing.

Key words

Breast cancer control, breast cancer screening, stage distribution, developing countries, model, validation, CBE screening.

Abbreviations used

LMICs: low- and middle-in income countries; CBE: clinical breast examination; MSTs: mean sojourn times; AJCC: American Joint Committee on Cancer; DCIS: ductal carcinomas in situ.

Introduction

Breast cancer is the most frequent cancer occurring in women in both high-income countries (HICs) and low- and middle-income countries (LMICs), and is a major public health problem. In 2008, breast cancer was responsible for about 485,000 deaths worldwide, and some 1.4 million new cases of breast cancer were diagnosed. The incidence and mortality rates of breast cancer are expected to rise in most LMICs in the coming years [1].

Early detection, followed by appropriate treatment, is currently the most effective strategy to reduce breast cancer mortality [2]. Mammography screening is widely used for early detection in high income countries (HICs) and is generally applied to women aged between 50 and 70 years. Although the benefits and harms of mammography screening are still being debated, the impact of mammography screening on breast cancer mortality in HICs seems to be about 20% to 30% [3-5].

LMICs could also establish early detection strategies based on mammography screening or perhaps clinical breast examination (CBE) screening [6]. So far, however, the impact and practicability of screening strategies in LMICs is largely unknown due to a lack of cancer registries and experimental studies [6-9]. In addition, extrapolating the impact of screening programs from Western populations to populations in LMICs is not a straightforward process due to the diversity in epidemiology, socio-cultural aspects, and the differences in the organization of health care systems.

While actions to control breast cancer seem essential in LMICs, it is not easy to make well-informed decisions on how to control the disease in these countries. For this reason, we propose a simple model to assess the performance of different modalities of breast cancer screening in LMICs and possibly their further impact. The model estimates the shift in the proportion of early vs. late stage breast cancers (i.e., stage shift) based on the expected performance rates in the screened population. Although the amount of stage shift cannot be straightforwardly linked to breast cancer mortality, it can be regarded as an important proxy for the performance of early detection programmes [8, 10-16]. Particularly in LMICs where the stage distribution of newly diagnosed breast cancer cases is often poor, the amount of stage shift is an essential performance indicator that could help LIMCs to decide on which breast cancer control programmes to implement.

The objective of this study was to provide a proof of concept for our model, to explain the model parameters and assumptions and to provide an example of its application to a LMIC. Our model is based on data from the Nijmegen Screening Program [17] and established screening theories [18, 19]. The model can assess the stage shift related to mammography and clinical breast examination (CBE) screening with different screening frequencies and age groups, relies on accessible data [20], and could be easily adopted in LMICs. The model could provide important information for LMICs on the potential performance and further impact of a breast cancer screening program.

Methods

Our model requires three steps to estimate the shift in the proportion of early vs. late stage breast cancers (i.e., stage shift) related to mammography screening. Firstly, we calculate the proportional performance rates (i.e. index number Z) based on observations from the Nijmegen Screening Program [17, 21]. Secondly, we assess the association of Z and the amount of stage shift observed in the Nijmegen Screening Program. Thirdly, we hypothesize how Z could be used to estimate the stage shift as a result of breast cancer screening in other countries.

Step one – calculating the detection rates and "Z"

This step involves calculating the age-specific proportional detection rates (5-year age groups) [18]. These detection rates will then be used to calculate Z, a theoretical measure for the proportion of screen-detected breast cancers out of the total number of incident breast cancer cases per year (proportional performance rate) in a certain area or country. We hypothesize that Z, which accounts for the local screening and population characteristics, can be used to estimate the stage shift (shift in the proportion of early vs. late stage breast cancers), and can thus predict screening performance.

Mathematical framework

We used the following parameters to calculate proportional performance rates; targeted age groups, age-specific incidence, frequency of screening, age-specific mean sojourn times, age-specific sensitivity of the test, age-specific attendance rates, and age-specific population (Box 1). These parameters are explained in more detail below and in Appendix A, and relate to each other according to equations 1 through 4. These equations were adopted from Duffy et al [18] and adjusted for the addition of the parameters attendance, coverage by invitation, and the fraction of prevalent screens (i.e., A, C and ps) in equations 2 and 3. The summation of proportional performance rates of each 5-year age group will eventually result in a Z, (Equation 4).

Box 1. Parameters used

Parameters:

MST = Mean sojourn time of mammography (MST1) or CBE (MST2)
S = Sensitivity of mammography (Sm) or CBE (Scbe)
r = Screening frequency
λ = Transition rate from preclinical to clinical disease (1/MST)
I = Background incidence in situation without screening
A = Attendance rate
C = Coverage by invitation rate
ps= Fraction of prevalent screens
Z = Proportional performance rate (Index number)

Equation 1: Detection rate at prevalent (first) screens (P);

$$P = MST \times S \times I \times A \times C$$

Equation 2: Detection rate at incident (subsequent) screens (Q);

$$Q = \frac{S \times (1\text{-}e^{-\lambda r})}{\lambda(1 - 1\text{-}S)e^{-\lambda r})} \times I \times A \times C$$

Equation 3: Total 1-year detection rate (T);

$$T = \left(\frac{Q}{r} \times (1\text{-}ps) \right) + (P \times ps)$$

Equation 4: Proportional performance rate (Index number Z);

$$Z = \frac{\sum T_{\text{age groups screened}}}{\sum I_{\text{all age groups}}}$$

Estimates of input parameters

Most parameters used to calculate Z are true observations from the Nijmegen Screening Program. Detailed information on the Nijmegen Screening Program was retrieved from the department for Health Evidence of the RadboudUMC, Nijmegen. Essential information on this screening program has been recorded since 1975, including the age-specific target groups, attendance, referrals, incident and prevalent screens, and invitation intervals [21, 22]. The observed age-specific variables from each Nijmegen screening round (incidence [I], sensitivity of mammography [Sm], frequency [r], attendance [A], fraction of prevalent screens [ps]), were used in our equations to calculate Z for each screening round (n=16) (Table 1).

Not all parameters could be derived from the Nijmegen Screening Program. The mean sojourn times (MST1, MST2) and the sensitivity of CBE screening (Scbe) were based on the international literature [16, 18, 23-28]

Other unobserved parameters, such as the sensitivity of mammography (Sm) in age groups that were not included in the Nijmegen Screening Program, were derived from an assumed parameter distribution (Table 1). More detailed information on these parameters can be found in Appendix A. For the unobserved parameters that were predominantly based on the literature and were used in our model (MST1, Sm), we performed univariate sensitivity analyses.

Table 1. *Average age-specific parameters over 16 screening rounds (1975-2005)*

Screening ages	Population distribution	Incidence distribution (I)	Attendance rate (A)*	Sensitivity (Sm) Mammography**	Mean Sojourn Time (MST 1) mamgraphy [16, 18 #]	Sensitivity (Scbe) CBE [23##]	Mean Sojourn Time (MST 2) CBE [###]	Fraction of prevalent screens (ps)
0-14	19.13%	-	-	-	-	-	-	-
15-19	6.96%	-	-	-	-	-	-	-
20-24	7.28%	0.04%	0.92	2.99%	1.16	0.80	0.31 - 0.58	0.00
25-29	7.51%	0.23%	0.87	7.28%	1.35	0.78	0.36 – 0.68	0.00
30-34	7.56%	0.91%	0.84	13.36%	1.57	0.75	0.42 - 0.79	0.00
35-39	7.33%	1.94%	0.82	17.55%	1.83	0.72	0.49 – 0.92	0.54
40-44	6.89%	3.79%	0.82	32.28%	2.13	0.69	0.57 – 1.07	0.36
45-49	6.32%	5.69%	0.82	43.84%	2.48	0.64	0.66 - 1.24	0.47
50-54	5.88%	7.10%	0.82	53.16%	2.89	0.60	0.77 - 1.45	0.18
55-59	5.37%	7.51%	0.82	60.82%	3.37	0.55	0.90 - 1.68	0.08
60-64	4.83%	8.49%	0.80	67.24%	3.92	0.50	1.05 - 1.96	0.08
65-69	4.27%	9.80%	0.76	72.70%	4.56	0.44	1.22 – 2.28	0.10
70-74	3.75%	9.43%	0.70	77.39%	5.31	0.37	1.42 – 2.66	0.08
75-79	3.06%	10.65%	0.60	81.47%	6.19	0.31	1.66 - 3.09	0.09
80-84	2.16%	10.83%	0.47	85.05%	7.21	0.23	1.93 - 3.60	0.09
85-89	1.17%	9.81%	0.30	88.21%	8.39	0.19	2.25 – 4.19	0.00
90-94	0.43%	8.29%	0.08	91.03%	9.77	0.15	2.62 – 4.88	0.00
95+	0.10%	5.49%	0.00†	92.83%	10.87	0.13	2.92 - 5.42	0.00

Population and Incidence (I) numbers in this table are based on entire Dutch population, over the entire screening period (1975-2005)[24, 25]. Population distribution, attendance rate (A), sensitivity of mammography (Sm) and fraction of prevalent screens (ps), in this table are based on the observations of the Nijmegen Screening Program for the entire screening period (16 rounds). Age-specific attendance rate (A) and age-specific sensitivity of mammography (Sm), can be best explained by the following formulas;

** Cubic: $-8E\text{-}06 \times age^3 + 0.0011 \times age^2 - 0.0499 \times age + 1.566$ (R square: 0.991).*

*** $\leq$ age 35 S-curve: $e^{1.207+\left(\frac{-101.43}{age}\right)}$ / $\geq$ age 35 Inverse: $1.398+\left(\frac{44.622}{age}\right)$ (R square: 0.947).*

Estimates of age-specific mean sojourn times (MST1, MST2) and the age-specific sensitivity of CBE (Scbe) were base on the literature,[16, 18, 23, 26-30] and can be best explained by the formulas below. R squares in these formulas represent explained variance of age-specific estimates from literature vs. age-specific values estimated by formula.

 # Logistic: $\frac{1}{1.661 \times (0.97^{-age})}$ (R square: 0.741).

$\leq$ age 85 quadratic: : $-0.009x\ age^2 - 0.021 \times age + 84.906$ / $\geq$ age 85 Logarithmic 320.544+(-67.576 x LN(age)).

Lower range = $0.1608e^{0.0305 \times age}$ / higher range = $0.3021e^{0.0304 \times age}$

†imputed.

Step two - relating the calculated Z with the shift in breast cancer stage distribution

The second step relates the calculated Z, with the stage shift (i.e., the proportion of early vs. late stage breast cancers) as observed in the population of the Nijmegen Screening Program. For stage distribution, we followed the American Joint Committee on Cancer (AJCC) definition of cancer stages [29]. We outline our main assumptions below and explain the use of a linear regression model to assess the relationship between Z and the stage shift.

Hypothesis on stage shift – equal Z's, equal stage distributions

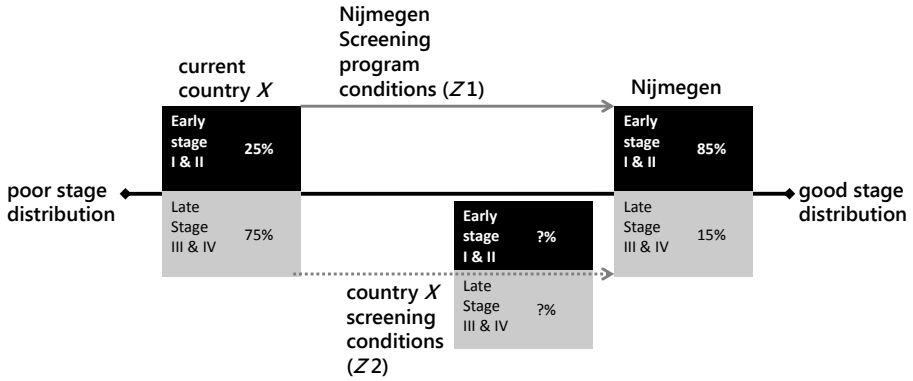
Our main hypothesis is that the calculated Z is related to the magnitude of the stage shift (i.e., the shift in the proportion of early vs. late stage breast cancer). If Z is related to these stage shifts, it can be used to estimate the potential stage shift of a certain breast cancer screening program that a LMIC considers for implementation. Figure 1 illustrates a hypothetical example of a country where no screening is applied and in which the current stage distribution is poor (about 25% of breast cancers detected in early stage [stages I and II]) [30]. When breast cancer screening is implemented, we expect a shift in stage distribution with more breast cancer patients presenting in the early stages I and II (85%) by following the experience from the Nijmegen Screening Program. The extent of this stage shift depends on the local screening and population characteristics, which are included in calculating Z.

We hypothesize that a country with an equal Z, as calculated in the Nijmegen Screening Program (i.e., equal proportional performance rates), will arrive at the same stage distribution as observed in the Nijmegen Screening Program (i.e., equal Z's - equal stage distributions). By adjusting the screening and population characteristics corresponding to the country under evaluation, we can calculate the countries' Z, and hence the extent of stage shift in this country when screening is applied (Figure 1).

Linear regression

We hypothesize that Z is linearly associated with the shift in breast cancer stage distribution (i.e., the proportion of early vs. late stage breast cancers). We use linear regression to predict the proportion with early stage breast cancer in the population (y), with Z as a single predictor (i.e., y = intercept + ß-coefficient * Z).

Figure 1. *Hypothetical stage shift assumptions*



When Z1 and Z2 are equal, both screening programmes perform equally well and the stage distribution is expected to be the same.

Step three – interpretation and use of regression coefficients

In the last step, we will use the linear regression model, but adjust the regression coefficients according to the conditions of a particular LMIC.

Adjusting regression coefficients to the context of a particular country

The linear regression model and its coefficients can be used to estimate the stage shift for a given Z. As explained above, we hypothesize that a country with a ***Z*** equal to that observed in the Nijmegen Screening Program will also have the same stage distribution as observed in the Nijmegen Screening Program (equal Z's - equal stage distributions). However, the countries' current stage distribution is likely different from the stage distribution in which the Nijmegen Screening Program started. The current stage distribution is represented by the intercept of our regression model. This means that the intercept of our regression model can vary by country, and we need to adjust the ß-coefficient according to these different intercepts. When the country has a Z equal to the Nijmegen Screening Program, the ß-coefficient should theoretically change to arrive at the same stage distribution. By changing the intercept (e.g., based on the current stage distribution of a country) while leaving the stage distribution unchanged, we can estimate the adjusted ß-coefficient for that country.

Results

Step one – calculating the detection rates and "Z" of the Nijmegen Screening Program

A total of 384,884 women were screened during the period from 1975 to 2005, and the breakdown of screening indicators and outcomes are presented in Table 2. The average attendance rate of this entire period was about 65%, with lower attendance rates during the period from 1979 to 1991 (attendance <60%). During this period, the targeted age groups for screening were relatively high. Of those who were screened, about 1% (0.95%) were recalled for further diagnosis and about one-third of these referred women were diagnosed with invasive breast cancer (0.36% of those screened). Of all screened women, about 0.06% were diagnosed with non-invasive carcinomas (DCIS), representing 15% of all screen-detected carcinomas (invasive and non-invasive). Over the entire screening period, 489 interval carcinomas were diagnosed in the participating women, representing about one-third (32%) of the total carcinomas that were found in the target population. The interval carcinomas also determined the screening sensitivity of roughly 65% for the entire screening period. In 1981, 1985, 1987, and 1989, the screening sensitivity was less than 55%.

Table 2 shows the estimated Z's per screening round in relation to the actual observed outcomes from the Nijmegen screening dataset. These Z's equal the proportional performance rates (Equation 4 in the methods section) and were calculated using the observed age-specific outcomes from the Nijmegen screening dataset. The start of the screening programme in 1975 and 1977 is represented by high Z's (99% and 67%, respectively) and high actual observed outcomes (95% and 93% in early stages, respectively).

Table 2. *Observed screening outcomes (1975-2005) of the biennial Nijmegen Screening Program*

	1975	1977	1979	1981	1983	1985	1987	1989	1991	1993	1995	1997	1999	2001	2003	2005	Total/ Average
Round no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	16
Age groups targeted	36-65	38+	40+	42+	40+	40+	40+	40+	45-70	47-70	49-70	49-70	49-75	49-75	49-75	49-75	N.A.
Women in target group	23,210	30,547	29,003	28,034	29,977	30,595	30,196	28,954	26,380	17,925	15,600	16,200	19,124	19,414	19,881	19,844	384,884
Women invited	23,210	30,547	29,003	28,034	29,977	30,595	30,196	28,954	26,380	17,925	15,600	16,200	19,124	19,414	19,881	19,844	384,884
Coverage by invitation (C)	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Women screened	19,703	19,786	16,632	15,111	16,173	16,484	16,483	15,222	13,203	12,613	11,249	11,726	13,205	14,189	14,913	15,183	241,875
% prevalent screens (ps)	100%	20.49%	3.72%	2.54%	18.87%	8.88%	8.21%	3.07%	2.25%	2.51%	3.15%	14.03%	14.96%	16.24%	13.78%	12.76%	15.34%
Attendance rate (A)	84.89%	64.77%	57.35%	53.90%	53.95%	53.88%	54.59%	52.57%	50.05%	70.37%	72.11%	72.38%	69.05%	73.09%	75.01%	76.51%	64.65%
Recalled	254	192	134	127	105	87	86	97	91	84	91	138	172	124	289	236	2,307
% recalled	1.29%	0.97%	0.81%	0.84%	0.65%	0.53%	0.52%	0.64%	0.69%	0.67%	0.81%	1.18%	1.30%	0.87%	1.94%	1.55%	0.95%
Invasive screening carcinomas	66	67	48	40	45	44	45	51	51	48	34	52	71	59	71	73	865
% invasive	0.33%	0.34%	0.29%	0.26%	0.28%	0.27%	0.27%	0.34%	0.39%	0.38%	0.30%	0.44%	0.54%	0.42%	0.48%	0.48%	0.36%
Non-invasive screening carcinomas (DCIS)	9	8	9	8	11	17	6	10	10	8	10	5	12	7	12	11	153
% non-invasive (DCIS)	0.05%	0.04%	0.05%	0.05%	0.07%	0.10%	0.04%	0.07%	0.08%	0.06%	0.09%	0.04%	0.09%	0.05%	0.08%	0.07%	0.06%
Interval carcinomas	32	35	30	35	26	34	41	42	28	22	16	24	33	27	35	29	489
Screening sensitivity (S)	67.35%	65.69%	61.54%	53.33%	63.38%	56.41%	52.33%	54.84%	64.56%	68.57%	68.00%	68.42%	68.27%	68.60%	66.98%	71.57%	63.74%
Cancers in women not invited)	69	50	51	58	51	53	70	71	84	67	91	99	118	110	119	103	1264
Programme sensitivity	39.52%	44.08%	37.21%	30.08%	36.89%	33.59%	28.85%	31.10%	31.29%	35.04%	24.11%	29.71%	31.98%	30.10%	31.56%	35.61%	33.17%

	1975	1977	1979	1981	1983	1985	1987	1989	1991	1993	1995	1997	1999	2001	2003	2005	Total/ Average
Stage I	69%	63%	52%	41%	47%	36%	38%	42%	35%	43%	38%	43%	42%	43%	37%	47%	45%
Stage II	26%	31%	32%	41%	42%	43%	46%	42%	38%	40%	46%	40%	39%	42%	46%	40%	40%
Stage III	4%	6%	13%	17%	12%	21%	14%	15%	24%	15%	16%	15%	18%	14%	16%	12%	15%
Stage IV	1%	1%	4%	0%	0%	0%	3%	1%	3%	2%	0%	1%	1%	1%	0%	1%	1%
% in early stage	95%	94%	83%	83%	88%	79%	83%	85%	73%	83%	84%	84%	81%	85%	83%	88%	84%
Index Z*	0.95	0.86	0.34	0.26	0.32	0.29	0.26	0.27	0.26	0.40	0.36	0.36	0.40	0.42	0.36	0.40	0.41

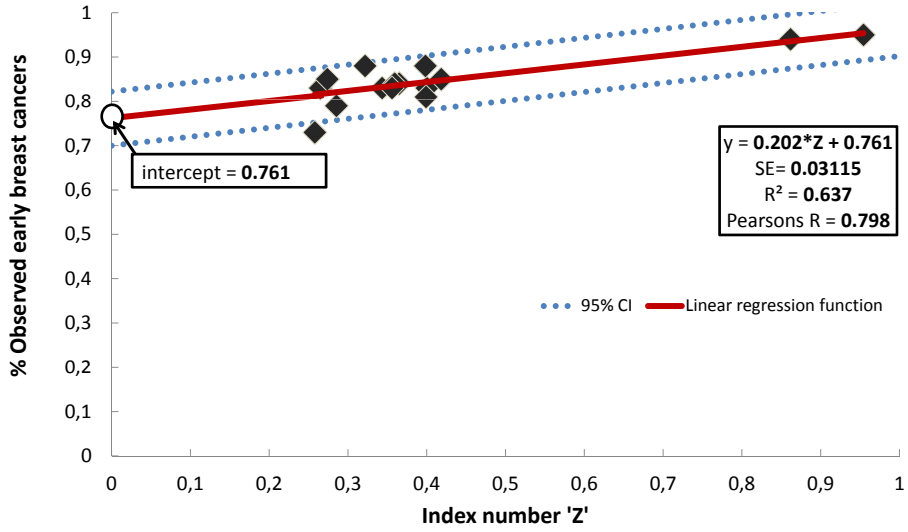
Screening sensitivity = (invasive screening carcinomas/[invasive screening carcinomas + interval carcinomas]); Programme sensitivity = (invasive screening carcinomas/[invasive screening carcinomas + interval carcinomas + cancers in women not invited]); Stage I to IV: breast cancer stages are based on AJCC staging atlas.[29] N.A. = not applicable.

**Index Z was calculated according to formulas as described in our methods section.*

Step two - relating the calculated Z with the shift in breast cancer stage distribution

The estimated Z's start to decrease in 1979 and remain at the same level until 1993, with some fluctuations. The observed outcomes during this same period, however, remain relatively high, which indicates a low correlation between Z and observed outcomes during these screening rounds. Nevertheless, the overall linear correlation between the Z's and the observed outcomes over the entire screening period (1975-2005) is significant (Pearson's r = 0.798). The results of our simple linear regression model are visualized in Figure 2. Our selected model has an explained variance (R square) of 0.637 and can estimate the proportion of breast cancers early stage (y) using Z with the following equation: $y = 0.761 + 0.202 * Z$ (p=0.000).

Figure 2. *Correlation of 'Z' and the percentage of early stage cases of screening rounds 1975–2005 and the corresponding regression function (values per round are presented in Table 2)*



Step three – interpretation and use of regression coefficients

Our results show that the proportional performance rates (Z's) are associated with stage shifts, and can therefore be used to estimate the stage shift (proportion of early vs. late breast cancer stages) as a result of breast cancer screening. In order to calculate the stage shift corrected for the current stage distribution of a country (i.e., different intercepts), the ß-coefficients will change according to the values in Table 3. Based on this table, countries could use the ß-coefficient depending on their current stage distribution. This ß-coefficient could then be used to estimate the stage shift resulting from a screening program based on the regression function and the calculated Z. A hypothetical example on how our model can be applied in a LMIC is available in the next section.

Table 3. *Regression coefficients under different starting conditions*

Intercept	Regression coefficient (β)	Proportion in early stage (y)	Confidence interval (CI) of estimate*
0.7500	0,2270	y = 0.75 + 0.2270 x Z	± 0.0611
0.7000	0,3404	y = 0.70 + 0.3404 x Z	± 0.0611
0.6500	0,4539	y = 0.65 + 0.4539 x Z	± 0.0611
0.6000	0,5674	y = 0.60 + 0.5674 x Z	± 0.0611
0.5500	0,6809	y = 0.55 + 06809 x Z	± 0.0611
0.5000	0,7944	y = 0.50 + 0.7944 x Z	± 0.0611
0.4500	0,9079	y = 0.45 + 0.9079 x Z	± 0.0611
0.4000	1,0213	y = 0.40 + 1.0213 x Z	± 0.0611
0.3500	1,1348	y = 0.35 + 1.1348 x Z	± 0.0611
0.3000	1,2483	y = 0.30 + 1.2483 x Z	± 0.0611
0.2500	1,3618	y = 0.25 + 1.3618 x Z	± 0.0611
0.2000	1,4753	y = 0.20 + 1.4753 x Z	± 0.0611
0.1500	1,5888	y = 0.15 + 1.5888 x Z	± 0.0611
0.1000	1,7022	y = 0.10 + 1.7022 x Z	± 0.0611

The proportion of breast cancer cases diagnosed in stage I and II in a particular country where no screening is in place can be interpreted as the intercept.

**95% confidence interval based on ± 2x standard deviation.*

Application of our model, example Colombia

The Ministry of Health (MoH) of Colombia, a middle-income country, is interested in providing an organized breast cancer screening programme as part of their national cancer control strategy. The country faces an increase of breast cancer incidence, with most women arriving in late stage (15%, 30%, 35%, 20% in stage I to IV respectively) having a vast impact on their budget for cancer treatment. The country is particularly interested in a biennial mammography screening or biennial CBE screening program, for women aged 40 to 65. The MoH would like to know the impact of these two screening options, in terms of stage shift, over a period of 10 years.

Step 1

Colombian population registers are used for populating our model [31], and incidence information is obtained from GLOBOCAN 20. These GLOBOCAN incidence rates are increased with an overall rate of 3% per year, and projected over their documented population to calculate the age-specific number of incident cases (I). The MoH of Colombia assumes that the sensitivity (S) of both mammography and CBE screening is generally 10% lower compared to the Nijmegen Screening Program, because of the relatively undertrained radiologists and practitioners They also expect the overall attendance to be about 10% lower (A) but assume no differences in natural history of the disease (MST, A). The number of prevalent screens (ps), those women that are eligible for their first screening round, is calculated from the population register.

The original parameters provided in table 1 were adjusted according to these local differences and, for a biennial screening frequency (r=2), the country estimates five index numbers (Z) (one for each screening round). The calculations of Z for the first two screening rounds (2010, 2012) are provided in table 4, using the formula's for P, Q, T and Z.

Step 2 and 3

Next, the Zs of all screening rounds (2010, 2012, 2014, 2016, 2018) are used to estimate the proportion of early vs. late breast cancer stages, according to the regression coefficients in table 3. As the current breast cancer condition of Colombia can be characterized by 45% of the patients presenting in early stage (15 % stage I + 30% stage II), the MoH uses the regression coefficients corresponding to the 45% intercept (0.9349). Hence, the regression formula is defined by: y =0.45 + 0.9349*index Z. The proportions of early breast cancer stages per screening round (y) can now be estimated using this regression formula. These estimations (Zs and percentage of early stage cases) are presented in Table 5.

Besides the proportions of early breast cancer stages, Table 5 also presents rough estimates of the possible stage distributions as a result of the two screening programmes. Further explanation on this optional calculation (Step 4) is provided in Appendix B.

Sensitivity analysis on parameter assumptions

Whereas most of the parameters used in our proposed model are based on actual observations, we investigated different mathematical functions for our key unobserved parameters in the Nijmegen Screening Program. These unobserved parameters are the age-specific mean sojourn times for mammography (MST1), and the sensitivity of mammography (Sm) in age groups that were not targeted by the program (i.e., under age 30 years and above age 75 years). The overall impact of varying these functions on our regression model can be found in Appendix Table C1. When using a logistic or S-curve function for MST1 (model B, E and F), the explained variance (R square) of our regression model is relatively high. For sensitivity (Sm), a combined S-curve and inverse function (model F) results in the highest R square. In our selected model, we therefore used a logistic function for estimating MST1, and combined an S-curve and inverse function for estimating mammography sensitivity (Sm). Age-specific mean sojourn times and sensitivity for CBE screening (MST2, Scbe), could not be analyzed in a sensitivity analysis because CBE screening is not part of the Nijmegen Screening Program and therefore observations are lacking.

Table 4. *Estimated index numbers (Z) for Colombia for (first two screening rounds only)*

Screening ages	Population[33]	Incidence[20]	Attendance rate (A)*	Sensitivity (S) mammography*	Mean Sojourn Time (MST) mammography	Sensitivity (S) CBE	Mean Sojourn Time (MST) CBE	Fraction of prevalent screens (ps)	P mammography	P CBE	Q mammography	Q CBE	Index Z mammography	Index Z CBE
2010, first screening round														
0-14	5,877	-	NA	NA	NA	NA	NA	NA						
14-39	8,959	636	NA	NA	NA	NA	NA	NA						
40-44	1,606	707	0.74	0.30	2.13	0.71	1.07	1	334	394	0	0		
45-49	1,459	909	0.74	0.41	2.48	0.64	1.24	1	676	533	0	0		
50-54	1,237	985	0.74	0.49	2.89	0.58	1.45	1	1,031	613	0	0		
55-59	971	892	0.73	0.56	3.37	0.53	1.68	1	1,234	579	0	0		
60-64	735	744	0.72	0.62	3.92	0.48	1.96	1	1,294	499	0	0		
65-69	549	717	NA	NA	NA	NA	NA	NA						
70-74	409	688	NA	NA	NA	NA	NA	NA						
75+	957	1,545	NA	NA	NA	NA	NA	NA						
	∑ 22,759	∑ 7,822							∑ 4,568	∑ 2,618	∑ -	∑ -	'Z'= 0.584	'Z'= 0.335

Screening ages	Population[33]	Incidence[20]	Attendance rate (A)*	Sensitivity (S) mammography*	Mean Sojourn Time (MST) mammography	Sensitivity (S) CBE	Mean Sojourn Time (MST) CBE	Fraction of prevalent screens (ps)	P mammography	P CBE	Q mammography	Q CBE	Index Z mammography	Index Z CBE
2012, second screening round														
0-14	5,794	-	NA	NA	NA	NA	NA	NA						
14-39	9,108	666	NA	NA	NA	NA	NA	NA						
40-44	1,616	732	0.68	0.30	2.13	0.72	1.07	0.398	138	163	87	109		
45-49	1,523	977	0.67	0.41	2.48	0.65	1.24	0		0	274	247		
50-54	1,320	1,082	0.66	0.50	2.89	0.59	1.45	0		0	380	282		
55-59	1,069	1,011	0.65	0.56	3.37	0.53	1.68	0		0	414	267		
60-64	806	841	0.63	0.62	3.92	0.48	1.96	0		0	379	222		
65-69	602	809	NA	NA	NA	NA	NA	NA						
70-74	439	760	NA	NA	NA	NA	NA	NA						
75+	1,139	1,895	NA	NA	NA	NA	NA	NA						
	∑ 23,414	∑ 8,773							∑ 138	∑ 163	∑ 1,533	∑ 1,289	'Z'= 0.190	'Z'= 0.157

*P: Detection rate at prevalent screens ( ). Q: Detection rate at prevalent screens Total 1-year detection rate T = . Proportional performance rate Z = . Screened age groups are 40 to 64 with biennial interval. * These parameters were reduced with 10% of the original values listed in Table 1.*

Table 5. *Interpretation of index numbers (Z) using our proposed model for Colombia*

Year of screening	'Z' mammography	Outcome of model*	Estimate of stage shift as a result of mammography screening		Rough estimate of stage distribution as a result of mammography screening**				'Z' CBE	Outcome of model*	Estimate of stage shift as a result of CBE screening		Rough estimate of stage distribution as a result of mammography screening**			
			% of cases in early stage (I &II)	% of cases in late stage (III &IV)	I	II	III	IV			% of cases in early stage (I &II)	% of cases in late stage (III &IV)	I	II	III	IV
Before screening			45%	55%	15%	30%	35%	20%	Before screening		45.0%	55.0%	15%	30%	35%	20%
2010	0.584	(0.45 + 0.9079*0.58) = 0.9766	97.3%	2.3%	54%	44%	2%	1%	0.335	(0.45 + 0.9079*0.335) = 0.7541	75.4%	24.6%	41%	34%	16%	9%
2012	0.190	(0.45 + 0.9079*0.190) = 0.6225	62.2%	37.8%	34%	28%	25%	13%	0.147	(0.45 + 0.9079*0.147) = 0.5835	58.3%	41.7%	32%	26%	27%	15%
2014	0.186	(0.45 + 0.9079*0.186) = 0.6189	61.9%	38.1%	34%	28%	25%	13%	0.142	(0.45 + 0.9079*0.142) = 0.5789	57.9%	41.1%	32%	26%	27%	15%
2016	0.180	(0.45 + 0.9079*0.180) = 0.6134	61.3%	38.7%	34%	28%	25%	14%	0.136	(0.45 + 0.9079*0.136) = 0.5734	57.3%	42.7%	32%	26%	28%	15%
2018	0.220	(0.45 + 0.9079*0.220) = 0.6497	65.0%	35.0%	36%	29%	23%	12%	0.156	(0.45 + 0.9079*0.156) = 0.5916	59.2%	40.8%	33%	27%	27%	14%

**Screened age groups are 40 to 64, with biennial screening interval. **Allocation of proportion in stage I & II: 0.55 (stage I), 0.45 (stage II). Allocation of proportion in stage III & IV: 0.65 (stage III), 0.35 (stage IV). Further explanation is provided in Appendix B.*

Discussion

We provide the first proof of concept for a model to estimate the potential impact of screening on the stage distribution of breast cancer. Our model is based on a comprehensive mathematical framework that employs important screening performance parameters. These parameters were, to the extent possible, derived from observations from the Nijmegen Screening Program comprising over 30 years of screening data (1975-2005) in various age groups. In this study, we propose a three step approach to assess the potential impact of biennial mammography screening on breast cancer stage shifts. This approach could also possibly be used to predict the stage shifts from CBE screening programs and mammography screening programs with alternative screening frequencies and age groups, for which we provided an example (Colombia). Our model could provide important information on the possible performance of breast cancer screening programs that LMICs could consider implementing.

Our results confirm that our model can be used to estimate the stage shifts (proportion of early vs. late breast cancer stages) based on proportional performance rates (Z's), using linear regression. Our regression model explains a high proportion of the variability in our data (R square: 0.637), and the observed stage shifts in the Nijmegen Screening Program are highly associated with the Z's (Pearson's R: 0.798). This provides a conceptual proof for the first two steps of our model, although these steps should also be confirmed in other countries with different screening datasets.

Based on the hypothesis that countries with screening programs that perform equally well will have an equivalent stage distribution (equal Z's - equal stage distributions), any country could use the regression model (step three). Theoretically, the regression coefficients of this model should be selected according to the current stage distribution of the country under study. However, whether our hypothesis (equal Z's - equal stage distributions) can be accepted and, hence, whether it is valid to use step three of our model to extrapolate this regression model and use it for any country (external validity) is not proven by this study. Further research in other settings should be performed to verify this hypothesis.

Our model can also be used to assess the impact of CBE screening as well as other low-cost screening modalities that might become available [9, 32, 33]. However, although CBE screening trials are executed in a number of LMICs such as India, Peru, and Vietnam [15, 28, 34, 35], these trials currently lack estimates on important screening outcomes, therefore, the estimated impact of CBE screening by our model should be interpreted carefully. In our model, we based the mean sojourn time (MST2) of CBE screening on an exponential growth model and assumed a range of preclinical- and clinical -detection sizes. Yet, these preclinical- and clinical -detection sizes and growth models are still being debated [36-38].

Also, the age-specific sensitivity of CBEs (Scbe) were adopted from Bobo et al. and corrected according to Sankaranarayanan et al. [25, 28], and the findings from these studies cannot be generalized to CBEs performed in other settings. Despite these differences, our CBE sensitivity estimates have been used in other modelling studies [39], and could initially be used to assess the impact of CBE screening in developing countries. Future research should investigate the MSTs and the sensitivity of CBEs and mammograms in LMICs.

Our model is based on the use of accessible data. Population registries exist in most LMICs, and population estimates could otherwise be obtained from other sources [31]. If appropriate cancer registries are lacking, LMICs could use GLOBOCAN estimates to acquire age-specific breast cancer incidence rates [1]. While the quality of GLOBOCAN information from most of the LMICs might not be of sufficient quality, this data often remains the only relatively unbiased source of information available on the profile of cancer. As in our example in Colombia (Appendix B), LMICs could also assume different estimates based on their current stage distribution, sensitivity, or attendance rates, and adjust the age-specific estimates provided in this study (Table 2). Although LMICs could easily adopt our model and adapt the estimates we provide, we suggest that when our model is used different assumptions on these estimates should be addressed through uncertainty analyses.

There are some important limitations of this study and our proposed model.
First, although the Nijmegen Screening Program comprises data from over 30 years, our results are based on 16 screening rounds. This may impact the overall accuracy of our model (internal validity) and the inclusion of data from more screening rounds may improve our regression model.

Second and mentioned previously, the Nijmegen Screening Program only includes a population screened by mammography with a biennial screening interval, and the extrapolation of our model to other settings (external validity) is not yet proven by this study. In addition, although there is no clear evidence of this, natural history parameters could differ in the breast cancer populations of LMICs [40].

Third, our model is based on average, age-specific parameters, and does not allow dynamic modelling or simulation of individual patients. Since we use averaged parameters, we may have less precise estimates compared with more advanced models. Nevertheless, advanced models rely on difficult mathematical approaches and require advanced information at the expense of their usefulness for policy makers [39, 41, 42], and few of these models have been tested or applied in LMICs.

Fourth, not all factors relating to health care access are accounted for in our mathematical model. The insurance status, level of poverty, rate of obesity, and the method of detection could also impact screening performance [43, 44], although these factors should be partly covered by selecting locally relevant attendance rates.

Fifth, our model does not provide much more insight on the harms and benefits of screening (e.g., impact on mortality, over-diagnosis, survival, false positives) [3], and can only be used for estimating stage distributions. An improved stage distribution can be the result of diagnosing additional stage I cancers, but does not necessarily mean a reduction of the absolute numbers of stage III-IV cancers and, correspondingly, a reduction of mortality from the disease. Higher proportions of breast cancers detected in the early stages are, hence, not straightforwardly linked to higher levels of averted breast cancer mortality. Moreover, if early detection is not followed by appropriate treatment, which could often be the case in LMICs, the indirect impact of screening on breast cancer mortality would also decrease. The impact of screening on breast cancer mortality should therefore not (directly) be assessed through our proposed model, specifically in LMICs were appropriate breast cancer treatment could be lacking. Despite this, estimating the stage distribution as a result of screening is nevertheless helpful for the selection of early detection programmes as the amount of stage shift is a useful performance indicator for a screening programme. This information could be of particular interest for LMIC's were stage distributions are often poor, the continuum of early detection, treatment and follow-up services is not always available, and hence the eventual impact of screening on breast cancer mortality is difficult to estimate.

Sixth, whether a proposed screening program is beneficial to a particular country, cannot merely be based on the outcomes of our model (i.e. the estimated stage shift). Multiple criteria such as effectiveness, budget impact, cost-effectiveness, safety, accessibility of disadvantaged populations or other equity considerations, are often considered in deciding this [45]. The trade-off between, for example, the costs and effects of the proposed screening program depends on the willingness to pay for a unit of effect (e.g. QALY/DALY) of a country and - even more - on the available budget. Previous experiences indicate that the budget for controlling breast cancer may increase two- or three-fold due to a screening program. The effectiveness, however, will increase between zero- and five-fold, dependent on the current stage distribution of a particular country [46]. Our model can be used to support this discussion, by estimating the potential stage shift of a proposed programme so the potential costs or effects of this program can be estimated. The interpretation of the amount of stage shift as a result of breast cancer screening is therefore not straightforward, though we believe that 60% of breast cancer cases in early stage should nominally be obtained through a breast cancer screening program.

The above limitations fit within our aim to provide broad indications on the performance and the potential impact of different screening options in LMICs, rather than providing very precise estimates.

In conclusion, we have developed a three step model to estimate the potential impact of screening on the stage shift of breast cancer. Our results show that our model can be used to estimate the stage shifts of the Nijmegen Screening Program, and provides proof of concept that it could theoretically be adapted to other settings with different characteristics. This is a promising and important step, although further research should investigate the extrapolation of our model to other settings and investigate the assumptions used in our parameters.

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APPENDIX A

Parameter estimates

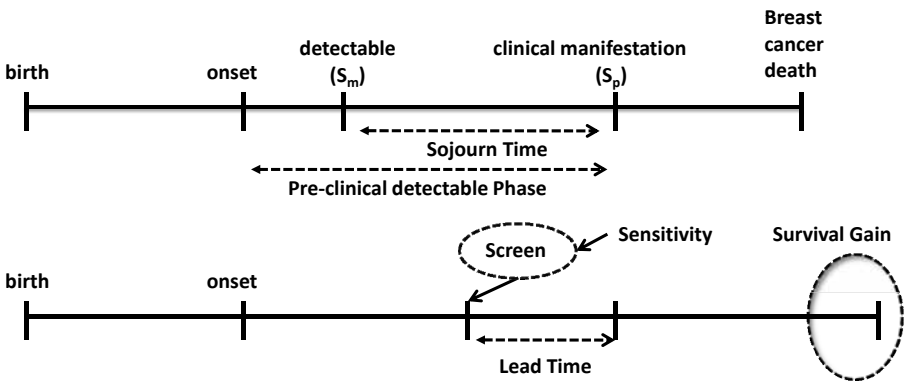
Most parameters used to calculate the proportional performance rate per screening round (index number Z) were based on true observations from the Nijmegen Screening Program, whereas other parameters were derived from the international literature (i.e. mean sojourn time [MST]) [1-3]. These parameters are discussed below.

Detailed information on the Nijmegen Screening Program was retrieved from the RadboudUMC, department for Health Evidence. Essential information on this screening programme has been recorded since 1975, including the age specific target groups. attendance, recalls, incident and prevalent screens, and invitation interval. The observed age specific screen detected carcinomas [4-8], interval carcinomas and residual carcinomas were for instance used to calculate age specific sensitivity for mammography (Table 1 of main document).

Natural history parameters (MST, A)

When describing the general natural history of breast cancer, we consider two important parameters in our equations; the mean sojourn time and lead time of breast cancer [9-11]. Both parameters are age-dependent and hence relate to the age-group in which screening takes place [12, 13]. The onset of breast cancer is dependent on the (natural) incidence in different age groups, while the mean sojourn time depends on both the aggressiveness (doubling time) of a tumour and the sensitivity of a test to detect the tumour. The lead time is also dependent on the ability to detect a cancer in the pre-clinically detectable phase (i.e. relates to the sensitivity of the test used) (Figure A1.1).

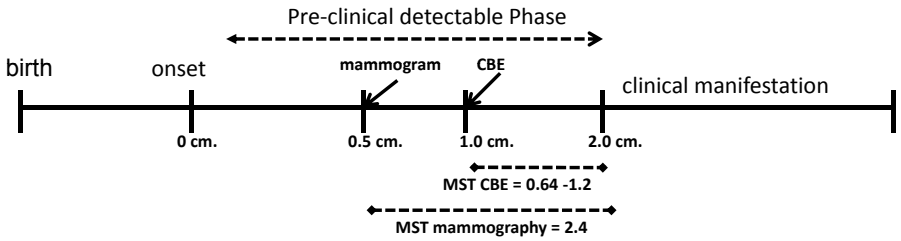
Figure A1.1. *Natural history representation of mean sojourn time (MST), lead time and sensitivity in non-screened vs. screened breast cancer populations [14].*



The age-specific sojourn time is the average time that it takes the cancer to grow from a size at which it becomes detectable by screening (Sm) to a size detectable clinically (Sp) (pre-clinical detectable phase). It depends on the average doubling time of the tumor in a certain age group and the ability of the screening test to detect the cancer. The lead time represents the earlier moment of detection due to screening with respect to the moment on which a tumor becomes clinically manifest (Sp). The ability of a screening instrument to detect cancer affects the sojourn and lead time. A survival gain is expected due to this earlier detection.

In future analyses, we could also use estimates of the MST(x) of clinical breast examination (CBE) by assuming that the growth rate of breast cancer can be described by an exponential function and by assuming standard average estimates of preclinical and clinical detection thresholds (i.e. the size of the cancer when it can be pre-clinically detected or clinically manifests) per age group. If we take for example a screening age of 40 to 49 years, which has a preclinical detection threshold (y) of 5 mm for mammography, and a MST (40-49) of 2.4 years. Then, let the preclinical detection threshold of for CBE be 10 mm and the clinical detection threshold 20 mm [3]. With these parameters we can estimate the MST (40-49) also for CBE, which has a preclinical detection threshold of 10 mm (y). Using the exponential formula for the preclinical detection threshold (y) of 10 mm: , gives us a MST (40-49) of 1.2 years for CBE (Figure A1.2, Table 1 of main document). However, multiple assumptions can be made on the preclinical detection thresholds of mammography (i.e. between 0.15 and 0.5 centimetre) and also the growth model for the growth rate of breast cancer (e.g. logistic, Gompertz, exponential functions)[12, 14]. When we would use a preclinical detection threshold for mammography of 0.15 centimetre, the exponential function would be y= This gives us, for a given preclinical detection threshold (y) of 10 mm, a MST of 0.64 years for CBE.

Figure A1.2. *Calculation of Mean sojourn time (MST) of CBE screens assuming a preclinical detection threshold of 1.0 cm. a clinical detection threshold of 2.0 cm. and an exponential growth rate [14]*



Demographical Parameters (l, population)

The annual number of breast cancer patients in a certain age-group can be estimated by using the age-specific incidence rate and the population at risk within the specific age-group (e.g. based on life tables). In our model we used the Dutch population and incidence statistics available from the Netherlands Statistics Institute (CBS) and the Dutch Cancer Registry (IKCnet) (Table 1 of main document) [15].

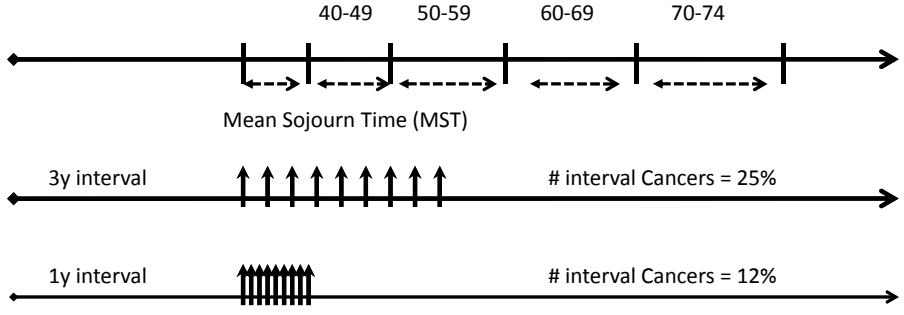
Health System Parameters (A, C)

We use two health system parameters that relate to the size of the implemented screening programme and the behaviour of the target population. The first indicator consists of the proportion of the target population invited with respect to the total target population (i.e. coverage by invitation rate, C). It could be possible for health program managers to implement a screening program only in a certain part of the country, for instance a single province. On a national basis, the potential impact of the screening program is then smaller as only a fraction of the total population is covered by this program. Our parameter C, accounts for this. The second parameter is based on the proportion of the population screened with respect to the total population invited (i.e., attendance rate A) (Table 2 of main document). This is an important parameter, which directly influences the potential impact of a screening program.

Screening Parameters (S, r, ps)

As outlined earlier, the sensitivity and specificity of a screening test are imperative for the efficiency of a screening program. Specificity is relating to the number of false-positives, thus more important when evaluating the harms of screening or screening costs-effectiveness. The sensitivity of a screening test can vary between settings because of differing machines and their calibration, reading experience and recall policies. The age-specific sensitivity estimates for mammography used in this study, were based on the interval and screen detected cancers of each screening round as observed in the Nijmegen Screening Program. The targeted age groups, proportion of prevalent screens and coverage by inviation were derived from the same dataset. The frequency of screening (e.g., annually, biennially or triennially) and the age groups targeted for screening will also impact the sensitivity and the overall effectiveness of the screening programme (Figure A1.3).

Figure A1.3. *Hypothetical influence of screening frequency (interval) in relation to mean sojourn time (MST) and sensitivity of a screening programme* [14]



Non-observed parameters

The observed age-specific variables from each Nijmegen screening round (sensitivity (S), frequency (r), attendance (A), fraction of prevalent screens [ps]), were used in our equations to calculate the Z of each screening round (n=16). As not all parameters were available or reliable for each age group (i.e. values for non-screened age groups or values years based on few observations), we estimated non-observed parameters using mathematical functions describing the distribution of the specific parameter, for a given age. The mathematical functions, derived from curve estimation models in SPSS, were selected according to the greatest R square and were based on the average age specific parameters of the entire screening period (i.e. grand means of the 16 screening rounds) (Table 1 of main document). For our unobserved parameters that were predominantly based on the literature and derived from an assumed parameter distribution (e.g., mathematical functions describing MST), we performed univariate sensitivity analysis (Table 4 of main document).

Additionally, we based the sensitivity of CBE screening on two studies. First, we obtained age-specific sensitivity estimates from Bobo et al[16]. Yet these age-specific sensitivity are based on an annual opportunistic screening program in the United States, and are therefore not representative for LMICs. We therefore reduced these estimates with 7.1%, according to the reported sensitivity of a large triennial CBE screening program in India [17]. The average difference in CBE sensitivity between these two studies used was 7.1% (58.8% vs. 51.7%).

Stage distribution

For stage distribution, we follow the American Joint Committee on Cancer (AJCC) definition of cancer stages. The original TNM breast cancer stage classification, derived from the entire population of the Nijmegen Screening Program, was reclassified to the AJCC stage distribution (stage I, II, III, and IV) [18]. This includes the invasive screening carcinomas. interval carcinomas and the carcinomas of non-targeted and non-participants (Table 2 of main document). This table also presents the proportions of early stage (AJCC stage I and II) and late stage (AJCC stages III and IV) breast cancers per screening round.

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APPENDIX B

Step 4: optional

Distribution of stage I to IV among estimated stage shift

Besides using our model for estimating stage shifts, it could also be used to estimate the breast cancer stage distribution (I, II, III and IV breast cancer stages). The average proportion of stage I and II among early stage (53% stage I, 47% stage II) and stage III and IV among late stage breast cancers (93% stage III, 7% stage IV) from the Nijmegen Screening Program (table 1 of main document), could hypothetically be used to reallocate stage I to IV over the proportions of late ***vs.*** early stages as estimated by our model. However, this distribution probably different in other countries based on variations in breast density, screening frequencies and referral policies of the adopted screening program [1-4]. If we would base this distribution on the several other countries that adopt organized screening programs, we could generally expect about 55% of the early breast cancer stages in stage I and 45% in stage II. For the late stages, this is probably 65% in stage III and 35% in stage IV, respectively (Appendix table B1). Although this is a rough approach, LMICs could use these approximated distribution rules to further estimate the stage distribution resulting from their screening activities (see Table 5 of main document).

Appendix table B1. *Stage distribution of breast cancer cases based on mammography screening in a number of high-income countries*

	Early		Late	
	Stage I	Stage II	Stage III	Stage IV
Nijmegen (this study)	53%	47%	93%	7%
NCDB (2010) [3]	63%	37%	69%	31%
New Hampshire 1998-2004 [5]	61%	39%	69%	31%
Germany (1996-2007)[1]*	71%	29%	-	-
BCSC (1994-2008) [6]	72%	28%	-	-
Netherlands 2003-2009 [7]*	50%	50%	74%	26%
Norway 1996-2005 [1]*	64%	36%	45%	55%
Belgium (Flemish) 2008 [8]*	62%	38%	56%	44%
Switzerland. Ticino 1996-2007 [9]*	50%	50%	66%	34%
Czech Republic. 2010 [10]*	53%	47%	71%	29%
France 2004-2008 [11]*	56%	44%	64%	36%
Slovenia 2009 [12]*	55%	45%	86%	14%
England. Northern. Yorkshire 1998-2000 [13]	45%	55%	61%	39%
East England 2006-2009 [14]	48%	52%	64%	36%
Scotland 2010-2011 [15]	53%	47%	64%	36%
Expected based on 2 year screening interval programs only (*) (rounded off)	55%	45%	65%	35%

NCDB = National Cancer Data Base; BCSC = Breast Cancer Surveillance Consortium. Stage distributions of NCDB and BCSC (United States) are based on opportunistic screening programmes and therefore not taken into account. Data from the United Kingdom are based on triennial screening programmes.

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3

CHAPTER

Costs, effects and cost-effectiveness of breast cancer control in Ghana

If things are getting easier, maybe you're headed downhill

(Ghanaian proverb)

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Abstract

Objective

Breast cancer control in Ghana is characterized by low awareness, late stage treatment and poor survival. In settings with severely constrained health resources, there is a need to spend money wisely. To achieve this and to guide policy makers in their selection of interventions, this study systematically compares costs and effects of breast cancer control interventions in Ghana.

Methods

We used a mathematical model to estimate costs and health effects of breast cancer interventions in Ghana from the healthcare perspective. Analyses were based on the WHO-CHOICE methodology, with health effects expressed in disability-adjusted life years (DALYs), costs in 2009 United States dollars (US$), and cost-effectiveness ratios (CERs) in US$ per DALY averted. Analyses were based on local demographic, epidemiological and economic data, to the extent this data was available.

Results

Biennial screening by clinical breast examination (CBE) of women aged 40-69 years, in combination with treatment of all stages, seems the most cost-effective intervention (costing $1,299 per DALY averted. The intervention is also economically attractive according to international standards on cost-effectiveness. Mass media awareness raising (MAR) is the second best option (costing $1,364 per DALY averted). Mammography screening of women of 40-69 years (costing $12,908 per DALY averted) cannot be considered cost-effective.

Conclusions

Both CBE screening and MAR seem economically attractive interventions. Given the uncertainty on the effectiveness of these interventions, only a phased introduction of these interventions, together with a careful monitoring and evaluation, is warranted. Moreover, their implementation is only meaningful if the capacity of basic cancer diagnostic, referral and treatment and possibly palliative services is simultaneously improved.

Introduction

Breast cancer is a major public health problem in Ghana. It is the most common type of cancer among Ghanaian women in terms of mortality and prevalence and over 20,000 disability adjusted life years (DALYs) are lost every year due to breast cancer [1]. Ghana is facing a relatively high mortality to incidence ratio and it is expected that the incidence will increase in Ghana in the years to come [2, 3]. (Table 1)

Currently, Ghana lacks a formal breast cancer control policy. Breast cancer treatment guidelines are absent and treatment involving radiotherapy is only available in Ghana's two largest cities creating important geographic barriers to access. Also financial barriers exist: although breast cancer diagnosis and treatment are covered by Ghana's National Health Insurance (NHIS), only 34% of the Ghanaian population was enrolled in 2010 [4]. Available studies on breast cancer in Ghana typically report poor stage distribution, survival and awareness. They furthermore indicate that knowledge, beliefs and social stigma of Ghanaians are important determinants of the late stage presentation of breast cancer [5-8]. These poor conditions point out the need to improve breast cancer control policy in Ghana, and address the needs of Ghana's relatively young female population.

Given its limited health care resources, Ghana needs to spend money wisely and only fund those interventions that provide value for money. Cost-effectiveness analysis (CEA) is a tool that systematically compares costs and effects of health interventions and that can guide policy makers in these decisions. However, the evidence base on cost-effectiveness of cancer control in Ghana – or any other low-income country – is scarce [9, 10]. International literature on the costs and health effects of breast cancer control focuses mainly on high-income countries and is difficult to extrapolate to low-income countries due to differences in context. Screening programs in African countries, could for example use different tools and target different age groups than programs in Western settings.

This paper responds to the following research question: 'From the healthcare perspective, what are the costs, health effects, and cost-effectiveness of breast cancer control interventions in Ghana, and what is the optimal mix of interventions to maximize population health?' We used an established and previously published model by Groot et al. (2006) on the cost-effectiveness of breast cancer control in six world sub-regions, and adapted it to reflect the demographic, epidemiological and economic context of Ghana to the extent possible.

Table 1. *Age distribution of breast cancer incidence and mortality in Ghana*

Age groups	Female population*	Incidence (/100,000)	Number of incident cases (%)	Mortality (/100,000)	Number of deaths (%)	Mortality/ incidence ratio
0 to 14	4.605.974	0.1	5 (0.2%)	0.0	0 (0.0%)	n/a
15 to 29	3.145.512	1.0	31 (1.1%)	0.4	13 (0.7%)	0.40
30 to 44	2.013.112	31.7	638 (22.5%)	11.3	227 (12.3%)	0.36
45 to 59	1.231.140	80.1	986 (34.8%)	53.2	655 (35.3%)	0.66
60 to 69	482.535	104.5	504 (17.8%)	84.4	407 (22.0%)	0.81

Source: WHO Global Burden of Disease data, 2004 update.

**Based on population Ghana in 2009.*

Methods

General approach

We used WHO-CHOICE standardized methods in cost-effectiveness analysis - described in detail elsewhere - as a basis of our analysis [10, 11]. This approach compares all possible interventions to a situation where no interventions are available. This counterfactual acts as a reference to compare the cost and effects of existing and new interventions. The standardized method enables us to make comparisons of the costs and health effects across a wide range of competing interventions such as HIV/AIDS, malaria, and mental disorders [12].

Country adaptation

WHO-CHOICE has made a number of tools and methods available to adapt its regional results to the country level [13]. A study team, established in 2009, served as an expert panel to assess the mathematical model for its relevance in Ghana, define a meaningful set of interventions, identify data sources for the collection of country data, analyze results and interpret findings. The study team included representatives from the Ministry of Health (MoH), Ghana Health Services (GHS), breast cancer specialists, public health specialists and health economists.

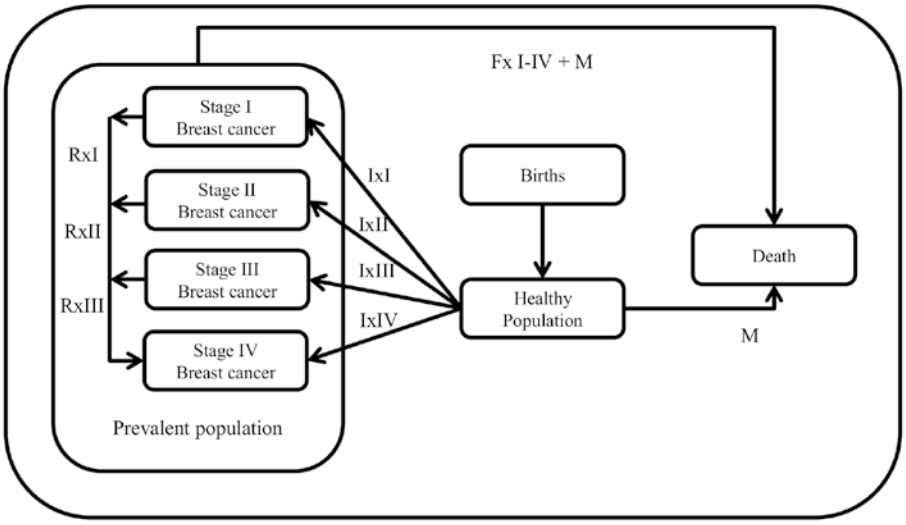
Mathematical model

The model structure is presented in Figure 1 [10]. This state transition population model simulates the development of the Ghanaian population and accounts for births, background mortality and breast cancer epidemiology of Ghana [14]. The model includes a healthy state, a deceased state, and stage I to IV breast cancer states following the American Joint Committee on Cancer (AJCC) [15]. The effectiveness of interventions is based on their effect on health state valuations (HSVs) and case fatality (treatment interventions), or stage distribution (awareness raising and screening interventions). Each intervention, individually and in combination, is then implemented for 10 years. Next, the model-population is followed over its life-time to include all health effects that occur after these 10 years.

Since the interventions are affecting both mortality (case fatality) and morbidity, intervention effectiveness is expressed in disability adjusted life years (DALYs). The difference in the total number of healthy years lived by the population between each scenario and the null-scenario gives the population health gains in DALYs averted.

We improved the initial model of Groot et al. (2006) by correcting HSVs for relapse, assuming that patients could only have relapse to stage IV at a constant rate. Additionally, we corrected stage-specific case fatality estimates, derived from the original study, for the addition of chemotherapy in stage I-II and mastectomy in stage IV according to the most recent Breast Health Global Initiative (BHGI) guidelines [16-19].

Figure 1. *Graphical representation of the model*



Graphical representation of the model showing the relationships between the different health states through the incidence rates of breast cancer (Ix1–Ix4), the different stage-specific case-fatality rates (corrected for progression) (Fx1–4) and the background mortality (M). Stage-specific relapse rates to stage IV were used to correct health state valuations only (Rx1–Rx3).

Interventions

The expert panel identified a set of 11 interventions that are relevant to breast cancer control in the Ghanaian context, all related to awareness raising, screening, treatment and palliative care (Table 2).

Table 2. *Definition and classification of individual interventions for breast cancer control in Ghana*

Treatment of individual stages	Down-staging interventions §	Palliative Care‖
Stage I treatment: lumpectomy with axillary dissection and radiotherapy.* Eligible patients receive tamoxifen† or chemotherapy.‡ [10, 16, 17]	Basic Awareness Raising (BAR): community nurses training program + opportunistic outreach activities by community nurses to raise breast cancer awareness and educate on breast self examination techniques (BSE) + enhanced media activities. [20]	Basic Palliative Care (BPC): palliative care-volunteers training program + home based visits by volunteers every fortnight + pain treatment through morphine, laxatives and palliative radiotherapy (8 Gy in 1 fraction) for eligible patients. [17, 20-22]
Stage II treatment: lumpectomy with axillary dissection and radiotherapy.* Eligible patients receive tamoxifen† or chemotherapy.‡ [10, 16, 17]	Mass-media awareness raising (MAR): BAR + mass media campaign. [20]	Extended Palliative Care (EPC): BPC apart from community nurses instead of palliative care-volunteers, pain treatment strengthened with anti-depressants, anti-emetics and zelodronic acid. [17, 20-24]
Stage III treatment: modified mastectomy followed by adjuvant chemotherapy‡ and radiotherapy.* Eligible patients receive tamoxifen.† [10, 17]	Biennial clinical breast examination (CBE) screening in asymptomatically women aged 40-69 years: community nurses training program + active outreach screening by community nurses + limited media activities. [20, 22]	
Stage IV treatment: adjuvant chemotherapy‡ and radiotherapy (10 Gy) + end of life hospitalization. Eligible patients receive total mastectomy and/or tamoxifen.† [17, 19]	Biennial mammography screening in asymptomatic women aged 50-69 years + limited media activities. [10]	
	Biennial mammography screening in asymptomatic women aged 40-69 years + limited media activities. [10]	

Some of these interventions do not yet exist in Ghana (e.g. mammography screening) but the expert panel judged them to be of potential benefit. The specific definition of interventions was based on consultations with the expert panel, WHO experts, BHGI guidelines, and the scientific literature [17, 18, 20, 21, 25].

The 11 interventions were combined to construct a total of 17 intervention scenarios. This includes the current Ghanaian situation in which patients of stages I to IV are treated at a 10% coverage level (as estimated by the expert panel). All other interventions are evaluated at a geographic coverage level of 80% (i.e. reaching 80% of those people who need services) according to the expert panel and standard CHOICE methodology.

Data sources

Health effects

Key components in the mathematical model are demography, breast cancer epidemiology, stage distribution, case-fatality and health state valuations. Data used to fill in these components are discussed in turn.

Demographic data was based on formal 2009 data from the government of Ghana [26]. We used Global Burden of Disease (GBD) estimates from 2004 for Ghana (personal communication), in the absence of more recent or detailed information. Information on the present stage distribution of breast cancer in Ghana was derived from records of the Korle Bu Teaching Hospital in Accra. The impact of the various screening interventions on this stage distribution was estimated on the basis of a simple model following Duffy et al. (2005) by using proportional detection rates and stage shifts from Groot et al. (2006). We calculated stage shifts in Ghana while accounting for locally relevant attendance rates (60% for screening programs), sensitivity of tests, sojourn time (reducing sojourn times for CBE by one-third), and incidence and prevalence in different age groups [27-30]. The effectiveness of the mass media awareness raising intervention was based on the study by Devi et al. (2007) whereas we assumed that the basic awareness raising intervention (BAR) caused a 10% down-staging of late stage breast cancer cases. In the absence of reliable Ghanaian data, data on case-fatalities of breast cancer were based on Groot et al. (2006) and relapse rates on the literature [10, 16, 18, 19]. Health state valuations were based on the Global Burden of Disease study, and corrected for relapse to stage IV [1, 10, 16]. We assumed that the palliative care interventions affect health state valuations only [19, 21, 31, 32] – its effect was determined by the expert panel. The assumed impact of each intervention is listed in Table 3.

Table 3. *Case fatality rates, disability weights and stage distributions used for individual interventions*

Intervention	Case fatality rates*				Disability weights†				Stage distribution‡			
	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	% in stage I	% in stage II	% in stage III	% in stage IV
Untreated	0.020	0.063	0.15	0.30	0.068	0.071	0.073	0.090	2.3%	20.5%	50.0%	27.3%
Stage I treatment	0.006				0.068				2.3%			
Stage II treatment		0.039				0.070				20.5%		
Stage III treatment			0.093				0.072				50.0%	
Stage IV treatment				0.227				0.0730				27.3%
Basic Palliative Care (BPC)				0.227				0.0720				27.3%
Extended Palliative Care (EPC)				0.227				0.0715				27.3%
Current country specific situation	0.006	0.039	0.093	0.227	0.068	0.070	0.072	0.073	2.3%	20.5%	50.0%	27.3%
Basic Awareness Raising (BAR)	0.006	0.039	0.093	0.227	0.068	0.070	0.072	0.073	10.2%	20.1%	44.8%	24.8%
Mass media Awareness Raising (MAR)	0.006	0.039	0.093	0.227	0.068	0.070	0.072	0.073	21.1%	41.5%	24.1%	13.3%
Biennial CBE screening (40-69)	0.006	0.039	0.093	0.227	0.068	0.070	0.072	0.073	39.5%	30.2%	19.2%	11.1%
Biennial mammography screening (50-69)	0.006	0.039	0.093	0.227	0.068	0.070	0.072	0.073	42.0%	32.1%	16.4%	9.4%
Biennial mammography screening (40-69)	0.006	0.039	0.093	0.227	0.068	0.070	0.072	0.073	47.8%	36.5%	10.0%	5.7%

Current country specific situation: Current situation in Ghana with treatment coverage of 10%.

** Original estimates (Groot et al) were corrected for the addition mastectomy in stage IV and chemotherapy in stage I and II.* [10,16-19]

† Original estimates (Groot et al) were corrected for relapse to stage IV. Relapse rates were derived from Adjuvant Online. [10,16,17]

‡ Present stage distribution is based on Korle Bu hospital registry.

Effects of MAR derived from Devi et al. 20. Effects of screening interventions were based on stage shifts from baseline 10 to the stage distribution in the USA 18. Stage shifts were adapted by calculating relative differences in detection rates between USA and Ghana 25. Calculations included age specific incidence, prevalence 1, sojourn time 25, sensitivity 24 and attendance rates (75% in USA vs. 60% in Ghana).

Costs

Following standardized WHO-CHOICE methodology on CEA, we distinguished between patient-level and program-level costs [13]. We used an ingredients approach to costing analysis, in which quantities and prices are separately reported.

Unit costs of patient services were as much as possible based on the principles of micro-costing, including detailed resource utilization patterns and prices. Estimates of these were based on Ghanaian treatment practices and/or expert opinion and local inventories of prices (personal communication). In some instances, no detailed estimates were possible and costs were based on NHIS fees charged for services from public hospitals. As a last resort, where no local resource utilization patterns were known or fees were available, on e.g. lumpectomy, we used the WHO-CHOICE database on standard medical procedures [33]. From this database we obtained the standard procedure for lumpectomy, including a series of standardized quantities on supplies and equipment needs, clinician time, and protocols of care. These quantities were then multiplied by Ghanaian unit prices (salaries, drugs and equipment). Prices of traded (international) goods were based on the WHO-CHOICE database, and were marked-up for transportation and distribution. To estimate the total patient costs of interventions, we multiplied the costs of patient services with the number of patients requiring these services (Table 4). The total number of patients requiring treatment is an output of the mathematical model, whereas the proportion of patients that make use of stage specific services (e.g. diagnostics, surgery, systemic therapy) was estimated by the expert panel.

Program-level costs capture management, administrative, media and law-enforcement costs, and costs for training of healthcare personnel. These costs were based on interviews with program managers from GHS. Media and operating costs (i.e. prices for broadcasting, flyers, and posters) were based on local inventories of prices.

For all interventions, we also included costs of diagnostic tests for women presenting without breast cancer (i.e. the tested negatives of all stages) and assumed the ratio of tested negatives vs. tested positives to be 16.4:1 [34]. Single treatment scenarios also include the costs of diagnosing all other stages and, regarding screening interventions, we included costs for evaluating false positives [22, 34-37].

All costs were estimated in 2009 local currency (Ghana Cedis) and converted to U.S. dollars (US$) using the 2009 exchange rate (1 GHC = 0.701 US$). Both health effects (DALYs) and costs (US$) were discounted at an annual rate of 3%.

Table 4. *Average utilization of diagnosis and treatment services and unit costs per patient*

Procedure	Ingredients	Stage I	Stage II	Stage III	Stage IV	Relapse	PC	Unit cost per patient (US$)
Initial diagnosis and evaluation during treatment	No. of health centre visits	1	1	1	1	0		3.51*
	No. of hospital visits	3	3	3	3	3		5.26*
	Bilateral Mammography	1	1	2	0	-		54.88*
	Complete blood count	7	7	7	7	6		14.21*
	FNA or core needle biopsy	1	1	1	1	-		38.78*
	Liver function tests	8	8	8	8	7		6.20†
	Ultrasonography	1	1	1	1			20.69*
	Renal function tests	8	8	8	8	7		7.01*
	Bone scan	0	0	1	1	-		109.94*
	Chest X-ray	1	1	1	1	-		23.93*
	ECG	1	1	1	1	-		13.46*
Non-breast cancer evaluation	No. of health centre visits	2	2	2	2			3.51*
	Bilateral Mammography	1	1	1	1			54.88*
	Ultrasonography	0.28	0.28	0.28	0.28			20.69*
	FNA or core needle biopsy	0.02	0.02	0.02	0.02			38.78*
Treatment	No. of hospitalization days	2	2	6	6	6	6	10.52*
	No. of end of life hospitalization days				7	7	4.7	10.52*
	No. of OPD visits radiotherapy	30	30	30	30	30	1	5.26*
	No. of OPD visits chemotherapy	6	6	6	6	5.3	-	5,26*
	% receiving surgical intervention	Lumpectomy 40%	Lumpectomy 30%	Lumpectomy 10%	Lumpectomy -	Lumpectomy -	Lumpectomy -	156.38†
		Mastectomy 60%	Mastectomy 70%	Mastectomy 90%	Mastectomy 5%	Mastectomy 5%	Mastectomy 5%	604.45†

Procedure	Ingredients	Stage I	Stage II	Stage III	Stage IV	Relapse	PC	Unit cost per patient (US$)
	% receiving anesthesia	100%	100%	100%	5%	5%	5%	136.77†
	% receiving radiotherapy	40%	30%	100%	10%	60%	-	37.48 per 2Gy†
	% receiving endocrine treatment	100%	100%	100%	40%	40%	-	0.28/day*
	% receiving chemotherapy	0%	20%	60%	60%	80%	-	405.71* (per 4 cycles)
	% receiving boost radiotherapy						41%	37.48†
	% receiving home based visits						75%	3.51/visit*
	% receiving morphine						84%	1.47/day*
	% receiving laxative						50%	4.91/day*
	% receiving Ondansetron						36%	3.51/day*
	% receiving Amitriptyline						41%	0.02/day*
	% receiving Zelodronic Acid						30%	108.71/day*

PC: Palliative care (substitutes stage IV treatment). Chemotherapy: 4 cycles of doxorubicin and cyclophosphamide , supplemented with dexamethasone (AC regimen). Endocrine treatment: daily dose of 20 mg.Tamoxifen for 5 years. Radiotherapy: 50 Gy given in 25 fractions of 2 Gy. Boost radiotherapy: 1 fraction of 10 Gy. Morphine: 40ml/54sdays. Laxatives: 35mg/54 days. Ondansetron: 8mg/day. Amitriptyline: 75mg/day. Bisphosphonates: 5 mg zelodronic acid/day.

** Unit costs derived from different sources. Local unit prices derived from public (university) hospital, combined with information from WHO-CHOICE (South African) database [30].*

† Unit costs completely derived from WHO-CHOICE (South African) database in 2000 US$. First corrected for IMF (world) inflation 2000-2009 (1.423) , then the 2009 GHC/US$ exchange rate was used (0.701)

Note: Program costs and costs for follow-up and screening procedures are not presented in this table.

Cost-effectiveness analysis

Average cost-effectiveness ratios (ACERs) are calculated for each intervention by dividing its total number of DALYs averted by its total costs. Using a standard approach, we identified the set of interventions a region should purchase to maximize health gains for different budget levels. The order in which interventions would be purchased is called an expansion path and is based on the incremental costs and health effects of each intervention compared to the last intervention purchased. Only interventions that are both more effective and less costly than other (combinations of) interventions are considered on this expansion path – and these are labelled 'dominant' interventions. The incremental cost-effectiveness ratios (ICER) for those interventions are calculated by dividing the incremental costs by the incremental health effects. WHO-CHOICE defines interventions that have a cost-effectiveness ratio of less than one time the gross domestic product (GDP) per capita as very cost-effective, and those with a ratio that falls between one time and three times the GDP per capita as cost-effective [38]. In Ghana, this means that interventions that cost less than $649 per DALY averted can be considered very cost-effective, and interventions that cost between $649 and $1,947 can be considered as cost-effective.

Sensitivity Analysis

We performed a deterministic sensitivity analysis to assess the impact of key parameters on cost-effectiveness results. The baseline case fatality rates and HSVs were varied +/- 25%, the effect of down-staging interventions was reduced by 25%, and for CBE screening we also used effectiveness estimates from other studies [22, 39-41]. Furthermore, we used different sources for Ghana's current stage distribution and varied costs for outpatient visits and hospitalization (+/- 25%). In addition, we lowered attendance rates of screening interventions (-10%), the sensitivity of CBE and mammography tests (-25%), and the capacity utilization of machinery (-25%).

Results

Table 5 shows costs, effects and cost-effectiveness of the 17 intervention scenarios. The annual number of DALYs saved by the individual stage I to IV breast cancer treatments vary between 365 (treatment of stage I) and 1,860 (treatment of stage III). Combined together, these interventions can avert almost 3,800 DALY's. The addition of a palliative care program only adds very few DALYs.

Interventions to raise awareness, combined with treatment of all stages, avert between 5,600 and 9,500 DALYs. Biennial CBE screening averts around 12 500 DALYs, whereas biennial mammography screening can save between 13,185 and 14,580 DALYs (depending on the targeted age-group), all in combination with treatment of all stages.

With increasing intervention effectiveness, costs increase as well. The individual treatment interventions cost between $5.1 million (stage I) to $10.3 million (stage III) annually, and are among the least costly interventions. Basic and extensive palliative care cost $6.0 million and $8.3 million, respectively. With an annual cost of over $42.4 million, biennial mammography screening of women between ages 40 to 69 years, combined with treatment of all stages, is the most costly intervention.

The cost-effectiveness ratios (CERs) of the individual treatment interventions range between $5,012 (stage II treatment) and $16,824 (stage IV treatment) per DALY averted. Extended palliative care costs almost $22,000 per DALY averted.

Interventions to raise awareness and screening interventions, combined with treatment of all stages, are more cost-effective than the treatment interventions. The most cost-effective intervention for breast cancer control in Ghana is biennial CBE screening in women aged 40-69 years combined with treatment of all stages, which costs $1,299 per DALY averted. Mass media awareness raising ($1,364 per DALY averted) is slightly less cost-effective than CBE screening. Mammography screening interventions, in combination with treatment of all stages, cost between $2,163 and $2,907 per DALY averted.

Table 5. *Costs (US$), effects and cost-effectiveness of breast cancer control in Ghana*

	Intervention scenarios*	Patients per year	Annual treatment costs†	Annual program costs†	Annual training costs†	Annual total costs†	DALYs averted a year‡	ACER	ICER
1	Current country specific situation (10% coverage)	445	1,449,828	135,222	52,786	1,637,836	437	3,745	NA
2	Stage I treatment	81	4,794,800	353,406	25,843	5,174,049	365	14,173	NA
3	Stage II treatment	727	5,984,201	353,406	25,843	6,363,450	1,270	5,012	NA
4	Stage III treatment	1,778	9,936,648	353,406	25,843	10,315,897	1,860	5,547	NA
5	Stage IV treatment	970	5,893,621	353,406	25,843	6,272,870	373	16,824	NA
6	Basic Palliative Care (BPC)	970	4,979,912	1,011,392	45,225	6,036,528	374	16,133	NA
7	Extended Palliative Care (EPC)	970	7,202,892	1,024,824	45,225	8,272,941	375	22,032	NA
8	Treatment of stage I to IV	3,556	11,684,609	446,962	51,685	12,183,257	3,785	3,219	NA
9	Basic awareness raising (BAR)+ treatment of stage I to IV	3,556	11,532,296	1,324,972	64,607	12,921,875	5,624	2,298	NA
10	Mass media awareness raising (MAR)+ treatment of stage I to IV	3,556	11,010,702	1,844,944	64,607	12,920,252	9,473	1,364	NA
11	Biennial CBE screening (40-69) + treatment of stage I to IV	3,556	14,795,753	1,435,919	79,374	16,311,046	12,560	1,299	1,299
12	Biennial mammography screening (50-69) + treatment of stage I to IV	3,556	26,682,513	1,691,896	141,533	28,515,941	13,185	2,163	NA
13	Biennial mammography screening (40-69) + treatment of stage I to IV	3,556	40,499,576	1,751,124	141,533	42,392,234	14,580	2,907	12,908
14	MAR + BPC + treatment of stage I to III	3,556	10,538,750	2,582,414	83,989	13,205,153	9,521	1,387	NA
15	Biennial CBE screening (40-69) + BPC + treatment of stage I to III	3,556	14,389,915	2,124,102	98,756	16,612,773	12,561	1,323	NA
16	Biennial mammography screening (40-69) + BPC + treatment of stage I to III	3,556	27,114,060	2,721,859	194,608	30,030,527	13,187	2,277	NA
17	Biennial mammography screening (50-69) + EPC + treatment of stage I to III	3,556	40,290,127	2,455,957	194,608	42,940,693	14,581	2,945	553,616

ACER = Average cost-effectiveness ratio compared to the do nothing-scenario (US$ per DALY averted). ICER = Incremental cost effectiveness ratio, ratio of additional cost per additional life-year saved when next intervention is added to a mix (additional US$ per additional DALY saved). NA = Not applicable because intervention is less cost-effective than others.

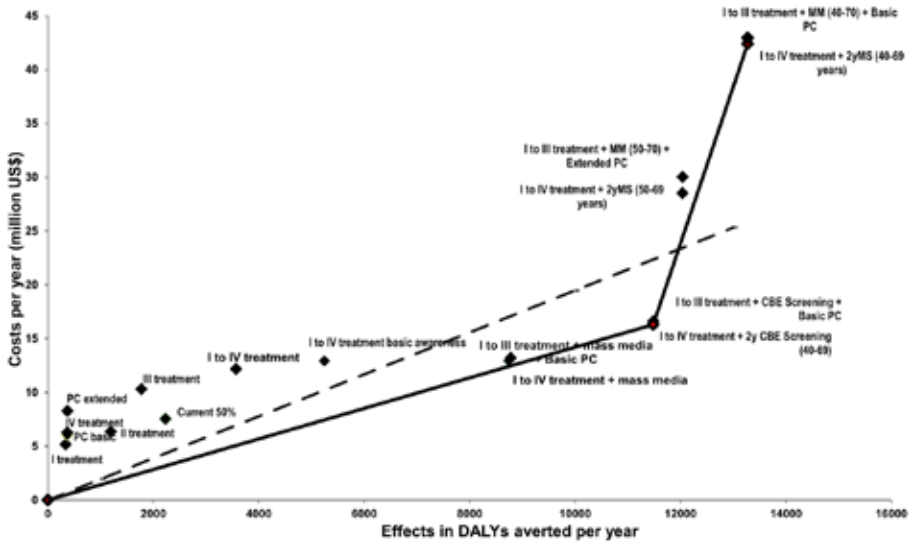
** Intervention scenarios are implemented at 80% coverage levels, except for scenario 1.*

† In 2009 US$ (1 GHC = 0.701 US$)

‡ DALYs, disability-adjusted life-years (age weighted, discounted)

Figure 2 shows the expansion path of breast cancer control, i.e. the order in which interventions should be implemented at different levels of resource availability. This path shows that biennial CBE screening of women aged 40-69 is the optimal choice (incremental cost per DALY of $1,299) at a cost of around $16 million, followed by mammography screening of women of 40-69 years (with an incremental CER of $12,908 per DALY saved) at a cost of $42 million, both in combination with treatment of all stages. The addition of basic palliative care to mammography screening and treatment of all stages would incur an incremental cost of $553,616 per DALY saved. The dotted line corresponds to three times the Ghanaian GDP per capita per DALY averted, and represents the suggested cost-effectiveness threshold as explained above. Both CBE screening and MAR plus treatment of all stages, combined with or without a basic palliative care program, are beneath this threshold. Note that MAR, because it is slightly less cost-effective than CBE, is not on the expansion path and would – strictly interpreted – not be a candidate for implementation. Yet, as these small differences are likely not policy relevant, we nevertheless consider MAR as a candidate for implementation.

Figure 2. *Cost-effectiveness of breast cancer interventions and expansion path according to ICER (Incremental cost-effectiveness ratio)*



*Dotted line represents the cost-effectiveness threshold of 3*GDP/capita/DALY averted (1,947 US$/DALY). In 2009 the Ghanaian GDP per capita was US$649.*

Sensitivity Analysis

Sensitivity analysis showed that our model is sensitive to alternative assumptions on case fatality rates and stage distribution, and to a smaller extent on sensitivity of tests, capacity utilization and attendance rates (Table 6). If higher case-fatality rates were assumed, representing poorer survival, the CER of awareness-raising and screening interventions would increase 14-46%. Lower case-fatality rates would result in a 12 to 44% decrease of these CERs. As our assumptions on current Ghanaian stage distribution are based on hospital records, we also considered alternative sources and these affected the CER of treatment stage I mostly (CER range -47% to +16%) and also the CER of awareness raising and screening interventions (CER ranges -26% to +22%).

Table 6. *Results of sensitivity analysis on average cost-effectiveness ratio (ACER)*

	Intervention scenarios	ACER	Alternative stage distribution A*	Alternative stage distribution B†	Case fatality rates +25%	Disability weights +25%	Costs outpatient visits +25%	Capacity utilization equipment -25%‡	Sensitivity of CBE and mammography -25%	Attendance rates screening programme 50%	Alternative effectiveness assumptions§
1	Current country specific situation (10% coverage)	3,745	4,694	3,297	6,522	4,325	3,825	3,885	-	-	-
2	Stage I treatment	14,173	6,714	4,208	16,427	16,000	14,466	15,056	-	-	-
3	Stage II treatment	5,012	10,175	7,467	10,181	5,797	5,138	5,282	-	-	-
4	Stage III treatment	5,547	8,675	5,523	11,078	6,280	5,745	5,793	-	-	-
5	Stage IV treatment	16,824	7,527	24,130	61,173	19,774	17,303	17,707	-	-	-
6	Basic Palliative Care (BPC)	16,133	6,028	24,258	58,388	16,032	16,536	16,992	-	-	-
7	Extended Palliative Care (EPC)	22,032	11,359	30,321	79,159	21,895	22,461	22,948	-	-	-
8	Treatment of stage I to IV	3,219	3,256	2,937	6,197	3,681	3,297	3,348	-	-	-
9	Basic Awareness Raising (BAR)+ treatment of stage I to IV	2,298	1,701	2,805	3,344	2,542	2,352	2,387	-	-	2,656
10	Mass media Awareness Raising (MAR)+ treatment of stage I to IV	1,364	1,077	1,577	1,681	1,468	1,390	1,415	-	-	1,503
11	Biennial CBE screening (40-69 years) + treatment of stage I to IV	1,299	1,047	1,478	1,499	1,385	1,351	1,352	1,451	1,409	1,274 -1,462
12	Biennial mammography screening (50-69 years) + treatment of stage I to IV	2,163	1,751	2,454	2,488	2,303	2,197	2,304	2,360	2,328	-
13	Biennial mammography screening (40-69 years) + treatment of stage I to IV	2,907	2,373	3,279	3,303	3,088	2,950	3,118	3,081	3,048	-
14	MAR + BPC + treatment of stage I to III	1,387	1,093	1,605	1,716	1,451	1,412	1,437	NA	NA	-
15	CBE screening (40-69) + BPC + treatment of stage I to III	1,323	1,066	1,505	1,528	1,380	1,374	1,376	1467,26	1,427	1,323-1,478
16	Mammography screening (40-69) + BPC + treatment of stage I to III	2,277	2,804	2,584	2,620	2,375	2,311	2,419	2,496	2,460	-
17	Mammography screening (50-69) + EPC + treatment of stage I to III	2,945	2,404	3,322	3,346	3,068	2,987	3,155	3,115	3,083	-

** Alternative stage distribution A, reflecting present Ghanaian situation, derived from breast clinic Kumasi (4% stage I, 7% stage II, 18% stage III, 70% stage IV).*

† Alternative stage distribution B, reflecting present Ghanaian situation, according to Groot et al. (9.4% stage I, 14.2% stage II, 58.0% stage III, 18.4% stage IV)[10].

‡ Mechanical equipment (e.g. mammography machines, CT, X-ray)

§ Alternative assumptions on effectiveness of awareness interventions (-25%), sensitivity of CBE 39, and stage shifts of CBE screening [35, 38, 39].

Discussion

Our analysis indicates that screening by CBE, in combination with treatment of all stages, seems the most cost-effective intervention for breast cancer control in Ghana. The intervention can detect cancer in an early stage and therefore allows early treatment with relatively high effects at low costs. The intervention costs around $1,300 per DALY averted, and seems cost-effective according to international thresholds on cost-effectiveness. MAR can also be considered cost-effective according to the same threshold, but mammography screening not.

Our study confirms the findings by Groot et al. (2006) that screening interventions are cost-effective and that early stage treatment is more cost-effective than late stage treatment. One difference is the relatively few number of patients with stage I breast cancer in Ghana, which renders treatment of stage I relatively less cost-effective (considering the relatively large fixed cost for testing all women presenting with breast cancer symptoms but do not have cancer). Our results are also in line with findings by comparable CEA studies on cancer control. When expressed in International Dollars (I$), CBE screening in Ghana would cost about I$2,750 per DALY averted and is in the same range of cost-effectiveness as cervical (ranging I$307 to I$100,075 per DALY) and colorectal cancer (ranging I$336 to I$15,548 per DALY) control options in the African sub-region [42].

This study leads to a number of observations on breast cancer control policy in Ghana. First, our study suggests that biennial CBE screening in women aged 40-69 years, combined with treatment of all stages, is economically attractive. This corresponds with findings from India, Egypt and Ukraine [22, 40, 43, 44]. However, it should be taken into account that the implementation of CBE screening is highly dependent on the availability of human resources, facilities and devices for proper diagnosis and treatment. There is also a considerable uncertainty on the effectiveness of CBE screening interventions, particularly regarding socio-cultural barriers: although most CBE screening studies show positive results on stage distribution, these interventions can easily fail when important aspects of education and information are neglected [6, 43, 45, 46]. Furthermore, implementation of this intervention would costs around $16 million per year, and raises concerns on affordability. With a total health expenditure of around $40 per capita (7.8% of total GDP) [47] the CBE screening would currently costs about $0.70 extra per capita (1.75 % increase) and seems only sustainable when combined with other programs (e.g. cervical cancer) and with long-term budgetary commitments. At this moment, a nationwide CBE screening program therefore seems a suitable option only in the long run. Pilot studies, in which the implementation of CBE screening is explored in e.g. the context of current primary healthcare structure, may be a first step. This could be followed by a phased introduction, in which the program is carefully monitored and evaluated.

Second, MAR is almost as cost-effective as CBE screening but requires a smaller budget (around $13 million) and could be an alternative strategy. However, there is only very limited evidence on intervention effectiveness, and our estimates must be interpreted with great caution [20, 48, 49]. As for CBE screening, the implementation of MAR is highly dependent on the availability of human resources and treatment services and can only commence in the long run upon careful evaluation.

Third, although treatment interventions are, on themselves, not cost-effective, they are relatively affordable and deserve higher priority if only a small budget would be available. The annual costs for treating all stages are far lower ($12.18 million) than those of screening options, and scaling-up treatment of all stages to a 80% coverage level, would already generate an almost ten-fold gain in DALYs annually. Moreover, treatment is an integral component of the continuum of care and essential to be scaled up if any intervention for early detection is implemented. A gradual increase in coverage of basic treatment services, along with improvements of referral systems should then be simultaneously established [45, 50].

Fourth, the need for pain treatment of stage IV patient is evident [25]. If management of stage IV patients entails basic palliative care, health effects slightly increase and costs slightly decrease (due to a reduction of hospitalization days). Hence, this form of palliative care is economically attractive and seems most meaningful. Extended palliative care costs much more, averts relatively few extra DALYs, and is therefore not recommended from an economic perspective.

Fifth, while biennial mammography screening is proven cost-effective in high-income countries, our analysis suggests it is not cost-effective in Ghana. Mammography screening would also require huge investments in equipment and human resources, demanding a considerable proportion of Ghana's health budget. Nevertheless, investments in mammographic services are still required for diagnostic purposes in Ghana, and mammography screening could become a relevant option if more resources would become available in the future.

Our study has a number of limitations. First, the national cancer registry in Ghana is not fully functional and local data on breast cancer stage distribution were derived from Korle Bu Teaching Hospital, Accra and Komfo Anokye Teaching Hospital, Kumasi. Since this is based on presenting patients rather than on all patients, this may not reflect reality and may have biased our estimates. Second, information on the epidemiology and case-fatality of breast cancer was not locally derived, but based on the GBD and observations in other countries. If e.g. poorer case-fatality rates would apply to Ghana, we expect CER estimates to worsen (Table 6). Third, in the absence of reliable data and following the requests from Ghanaian stakeholders, we did not include travel costs or productivity losses of patients seeking or undergoing care and only evaluated biennial screening options. Including these cost would have probably lead to increased cost generally, and particularly for women with advanced stage breast cancer [51, 52].

Fourth, data on costs and treatment regimes were derived from small-scaled, locally available sources or expert opinion, and may not be representative for the whole country. Fifth, evidence on the effectiveness of awareness raising, CBE and mammography screening in Ghana is absent. To arrive at Ghanaian estimates we used a model approach that showed face validity, confirmed by the expert panel in our study. Despite these limitations, results of our model show similarities with results from other models [9, 44]. Moreover, although our sensitivity analysis showed that CER ranges of several interventions are overlapping, our overall study conclusions remain the same. The above limitations fit within the overall aim of WHO-CHOICE analysis to provide broad indications of cost-effectiveness on a range of interventions to inform general policy discussions rather than to deliver precise estimates on a specific intervention. Nevertheless, these limitations indicate the need to improve the evidence base of decision-making in breast cancer control in Ghana.

In summary, our analysis suggests that breast cancer control in Ghana, in order to be efficient, should be oriented towards earlier detection. However, the provision of basic cancer diagnostic, referral, treatment and possibly palliative facilities are fundamental for breast cancer control along the continuum of care and should be established simultaneously with any intervention for early detection. A phased introduction of CBE screening or perhaps MAR, coupled with a careful monitoring and evaluation, could be a feasible option for Ghana and should be further explored.

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4

CHAPTER 5

Cost-effectiveness analysis of breast cancer control interventions in Peru

Gold, when beaten, shines

(Peruvian saying)

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Abstract

Objectives

In Peru, a country with constrained health resources, breast cancer control is characterized by late stage treatment and poor survival. To support breast cancer control in Peru, this study aims to determine the cost-effectiveness of different breast cancer control interventions relevant for the Peruvian context.

Methods

We performed a cost-effectiveness analysis (CEA) according to WHO-CHOICE guidelines, from a healthcare perspective. Different screening, early detection, palliative, and treatment interventions were evaluated using mathematical modeling. Effectiveness estimates were based on observational studies, modeling, and on information from Instituto Nacional de Enfermedades Neoplásicas (INEN). Resource utilizations and unit costs were based on estimates from INEN and observational studies. Cost-effectiveness estimates are in 2012 United States dollars (US$) per disability adjusted life year (DALY) averted.

Results

The current breast cancer program in Peru ($8,426 per DALY averted) could be improved through implementing triennial or biennial screening strategies. These strategies seem the most cost-effective in Peru, particularly when mobile mammography is applied (from $4,125 per DALY averted), or when both CBE screening and mammography screening are combined (from $4,239 per DALY averted). Triennially, these interventions costs between $63 million and $72 million per year. Late stage treatment, trastuzumab therapy and annual screening strategies are the least cost-effective.

Conclusions

Our analysis suggests that breast cancer control in Peru should be oriented towards early detection through combining fixed and mobile mammography screening (age 45-69) triennially. However, a phased introduction of triennial CBE screening (age 40-69) with upfront FNA in non-urban settings, and both CBE (age 40-49) and fixed mammography screening (age 50-69) in urban settings, seems a more feasible option and is also cost-effective. The implementation of this intervention is only meaningful if awareness raising, diagnostic, referral, treatment and basic palliative services are simultaneously improved, and if financial and organizational barriers to these services are reduced.

Introduction

In Peru and other Latin-American countries, cancers have become a pressing health concern over the last decades. Cancer incidence and mortality rates have been rising and will probably continue to rise as a result of population growth, aging, urbanization and lifestyle changes [1-4].

In Peru, the highest cancer burden is currently represented by stomach, cervix, breast, prostate and lung cancer. Breast cancer is, together with cervical cancer, the leading cancer among females in terms of mortality and incidence [5, 6]. Breast cancer has shown a persistent increase in incidence over the last decades, and many women present in advanced breast cancer stages. Efforts to control the disease in Peru are therefore essential (Table 1) [6, 7].

As a public response, the Peruvian Ministry of Health (MINSA) and allied institutions developed multi-sectoral cancer control strategies in 2006, focusing on prevention, education, early detection and expanding services for multiple cancers [8]. The strategic program, explicitly for breast cancer, consists of group and individual counseling in breast cancer prevention (women aged 18 to 64 years) as well as the promotion of annual mammography screening (age group 40-65). Furthermore, with the goal of reaching universal coverage, the Peruvian government introduced a universal health insurance law in 2009 and has also gradually been devoting more financial resources to cancer control [9-11].

Despite these developments, the implementing institutions face significant problems with the roll out of cancer control strategies. The coverage of breast cancer services is only partial and unequal, partly due to a fragmented health system, decentralization, and the unguaranteed financial resources [12]. In addition, only 51.8% of the population was insured (INEI 2008) and breast cancer treatment and rehabilitation, only partially covered by insurance, may require substantial out of pocket payments [13]. This may lead to important financial, cultural and geographical disparities in access to breast cancer care for many Peruvian women [14].

With this background, and with the rising cost of cancer control to the Peruvian healthcare system, MINSA is facing difficult choices on which breast effective cancer interventions to provide and at which cost they can be sustained for the long term. Also, given its limited health-care resources, Peru needs to spend money wisely and fund interventions that provide best value for money. Cost-effectiveness analysis (CEA) is a tool that systematically compares costs and effects of health interventions and that can guide policy makers in these decisions. Results from CEAs can for example be used to improve the general planning of strategies, or to strengthen certain breast cancer strategies by demonstrating their value for money. So far, CEAs on breast cancer interventions have not been conducted in Peru [15], hence, important information on efficient breast cancer control strategies is currently lacking.

To support breast cancer control in Peru, this study aims to explore and report the cost-effectiveness of different breast cancer control interventions relevant for the Peruvian context. In this paper, we provide an outline of the most efficient and feasible interventions for breast cancer control in Peru from the healthcare perspective.

Table 1. *Age distribution of breast cancer incidence and mortality in Peru*

Age groups	Female population (2005)*	Incidence rate per 100.000)*	Number of incident cases (%)	Mortality rate (per 100.000)*	Number of deaths (%)	Mortality / incidence ratio	Current stage distribution (AJCC)**
0-4	1,382,448	0.0	0 (0%)	0.0	0 (0%)	n/a	Stage I
5-14	2,860,994	0.0	0 (0%)	0.0	0 (0%)	n/a	7.04%
15-29	3,801,363	1.28	49 (1.4%)	0.25	10 (0.5%)	0.20	Stage II
30-44	2,736,393	31.69	867 (24.2%)	9.66	264 (12.7%)	0.30	36.44%
45-59	1,654,473	85.79	1419 (39.6%)	46.22	765 (36.7%)	0.54	Stage III
60-69	630,326	85.17	536 (15.0%)	64.45	406 (19.5%)	0.76	43.48%
70-79	400,815	121.59	487 (13.6%)	104.57	419 (20.1%)	0.86	Stage IV
80+	142,471	158.61	226 (6.3%)	153.32	218 (10.5%)	0.98	13.04%

**WHO Global Burden of Disease, 2004 update [7].*

***INEN 2007-2011 [12].*

Methods

General approach

Our standardized CEA methods, derived from WHO-CHOICE, are described in detail elsewhere and build on previous regional and country specific analyses of interventions to control breast cancer [16-20]. An important feature of this methodology is that all possible interventions are compared to a situation where no interventions are implemented. This counterfactual acts as a reference to compare the cost and effects of all possible interventions, and enables us to make comparisons across a wide range of competing interventions (e.g. tuberculosis, mental disorders, non-communicable diseases) [16, 21-24].

Breast cancer data and interventions

To select a set of breast cancer interventions relevant to Peru and to identify sources for cost and effectiveness data, a local study team was established during a stakeholder meeting in 2011. The team, consisting of representatives from the Ministry of Health (MoH), the national cancer institute (INEN), the social security network (EsSalud), PATH, and the World Health Organization (WHO/PAHO), could propose any type of breast cancer intervention. An assessment tool, to collect information on breast cancer programs and their coverage, finance, and epidemiology, was developed by the WHO and sent to the study team leader (INEN). Its results provided key data for our analyses and an overview of the current breast cancer activities in Peru [12].

From a standard set of breast cancer control interventions [17, 18], the study team identified a set of 15 interventions relevant to in the Peruvian context, all related to breast cancer treatment, early diagnosis, screening or palliative care (Table 2). The study team introduced a particular intervention of interest, relating to the diagnostic procedure of women with palpable masses detected through clinical breast examination (CBE) screening [25, 26]. This intervention aims at improving the capacity of early breast cancer diagnosis (i.e. confirmation by triple test) during CBE screening, by using upfront fine needle aspiration (FNA) first - instead of mammography first - at the primary healthcare level (Figure S1). In this way, the number of (technically more demanding) mammograms and core biopsies at the primary healthcare level could be reduced. The study team also adjusted standard treatment regimes of previous WHO-CHOICE analyses, and added therapies for HER2neu positive women (Trastuzumab). Furthermore, various combinations of screening age groups (40-69/40-64/45-69/45-64/50-69/50-64 years) and screening frequencies (annually/biennially/triennially) were introduced for the screening interventions. Additionally, the team defined different screening interventions specifically for rural areas (CBE screening vs. mobile mammography units in 40% of the total population) and urban areas (e.g. only fixed mammography units in 60% of the total population) according to the Peruvian urbanization rate (60%).

We combined the 15 interventions to construct a total of 94 intervention scenarios. This includes the current Peruvian situation in which patients of stages I to IV are treated at a 50% coverage level, along with preventive counseling (30% coverage) and opportunistic screening (15% coverage) [12]. Other interventions are evaluated at a geographic coverage level of 60%, 80% or 95% (i.e. reaching 95% of those who need services) according to standard CHOICE methodology.

Table 2. *Definition and classification of selected interventions for breast cancer control in Peru*

Treatment of individual stages	#	Awareness raising†	#	Screening†	#	Palliative Care‡	#
Stage I treatment: lumpectomy with axillary dissection and radiotherapy (33 fractions).* Eligible patients receive tamoxifen** [18, 27]	#4	Basic Awareness Raising (BAR): community nurses training program + opportunistic outreach activities by community nurses to raise breast cancer awareness and educate on breast self examination techniques (BSE) + enhanced media activities. [28]	#13	CBE screening: Clinical breast examination (CBE) screening (95% coverage) in asymptomatically women: community nurses training program + active outreach screening by community nurses + limited media and awareness raising activities. [29] • ages 40-69/40-64/45-64/45-69/50-69/50-64 • annual/biennial/triennial	#15-32	Standard Palliative Care (SPC): pain treatment through pain medication and anti-emetics, palliative radiotherapy (8 Gy in 1 boost) for eligible patients. Includes end of life hospitalization. No home based visits.[27, 30]	All except #11-12, 91-94
Stage II treatment: lumpectomy with axillary dissection (70%), or modified radical mastectomy (30%) followed by adjuvant chemotherapy*** and radiotherapy (33 or 25 fractions)* Eligible patients receive tamoxifen** or chemotherapy. ‡ [18, 27]	#5	Mass-media awareness raising (MAR): BAR + mass media campaign (weekly emissions) [28]	#14	Mammography fixed screening urban only : Mammography screening urban (57% coverage by fixed mammography units) in asymptomatic women + limited media and awareness raising activities. [17] • ages 40-69/40-64/45-64/45-69/50-69/50-64 • annual/biennial/triennial	#33-52	Basic Palliative Care (BPC): SPC + palliative care-volunteers training program + home based visits by volunteers every fortnight. Includes end of life hospitalization. [27, 30, 31]	#11, 91
Stage III treatment: modified radical mastectomy followed by adjuvant chemotherapy*** and radiotherapy (25 fractions).* Eligible patients receive tamoxifen.** [18, 27]	#6			Mammography screening fixed (urban) and mobile (rural): Mammography screening fixed (57% coverage by fixed mammography units + 38% coverage by mobile units) in asymptomatic women + limited media and awareness raising activities. [17] • ages 40-69/40-64/45-64/45-69/50-69/50-64 • annual/biennial/ triennialages [40]	#53-70	Extended Palliative Care (EPC): SPC+ BPC apart from community nurses instead of palliative care-volunteers, medication strengthened with anti-depressants, and bisphosphonates. Includes end of life hospitalization. [27, 30-32]	#12, 92-94

Treatment of individual stages	#	Awareness raising†	#	Screening†	#	Palliative Care‡	#
Stage IV treatment: adjuvant chemotherapy*** and radiotherapy (10 whole +3 boost fractions) + Standard Palliative Care. Eligible patients receive tamoxifen **[18,27]	#7			Mixed Screening: • Urban: Mammography screening urban (57% coverage by fixed mammography units) only in ages >50 / combined with CBE screening in ages <50 urban (57% coverage) in asymptomatic women + limited media and awareness raising activities.[17] • Rural: CBE screening all ages in non-urban areas (38% coverage) in asymptomatically women: community nurses training program + active out-reach screening by community nurses + limited media and awareness raising activities.[29] • ages 40-69/40-64/45-64/45-69/50-69/50-64 • annual/biennial/ triennial	#71-88		

Treatment of individual stages	#	Awareness raising†	#	Screening†	#	Palliative Care‡	#
Stage I to IV combined	#8-10			Upfront FNA (fine needle aspiration) after a positive CBE screen, only in combination with CBE screening: FNA training program for GP/medical officer at district hospitals + training of cytologists (2 per province/year). FNA samples are evaluated at district level, and eligible patients referred to provincial or national hospitals.[33]	#33-34, 89-93		
• without trastuzumab				• Combined only with the most cost effective biennial and triennial CBE screening intervention			
• with trastuzumab in all HER2 positives (stage I to IV).with trastuzumab in early stage HER2 positives (stage I and II only)							

** Radiotherapy generally includes a dose of 50 Gy given in 10-33 fractions or boosts on an outpatient basis*

*** Endocrine therapy consists of 20 mg. tamoxifen per day for 5 years.*

**** The (neo)adjuvant chemotherapy combination regimen consists of AC-Taxol: AC given 3-weekly for 4 cycles followed by paclitaxel given weekly for 12 weeks*

† Down-staging interventions cause a shift in stage distribution and are only modeled in combination with treatment of all stages (I to IV).

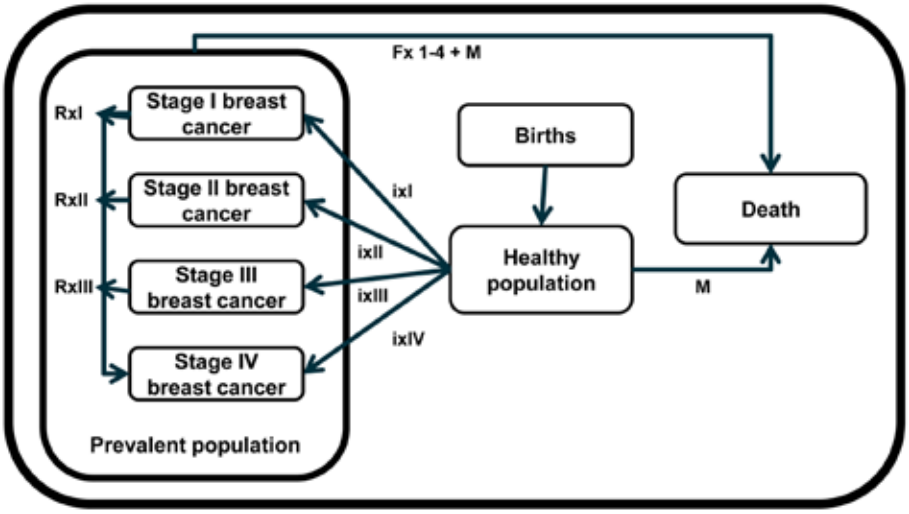
‡ Palliative care interventions BPC and EPC are only applied to stage IV patients, and substitutes Standard Palliative Care.

 # Scenario number in supplement (Table S2) and Figure 2

Mathematical model

The model structure is presented in Figure 1 and includes a healthy state, a deceased state, and stage I to IV breast cancer states following the American Joint Committee on Cancer (AJCC) [18, 34]. To assess health outcomes, WHO-CHOICE employs an epidemiological, population based approach. The national breast cancer epidemiology is entered into a state transition model, along with background birth, population, and mortality rates, to estimate the total number of disability adjusted life years (DALYs) experienced over the lifetime (100 years) of the Peruvian population [35]. The effectiveness of interventions is expressed in changes in case fatality (treatment interventions), health state valuations (HSVs), or stage distribution (awareness raising and screening interventions). Interventions are taken to be implemented for a period of 10 years, after which epidemiological rates go back to their counterfactual level of no intervention. The difference in the total number DALYs lived by the population between each scenario and the null-scenario gives the population health gains in DALYs averted. Consistent with the WHO Global Burden of Disease study, DALYs are discounted (at 3% per year) and age weighted.

Figure 1. *Graphical representation of the model*



Graphical representation of the model showing the relationships between the different health states through the incidence rates of breast cancer (Ix1–Ix4), the different stage specific case fatality rates (Fx1–4), and the background mortality (M). Stage specific relapse rates to stage IV were used to correct the disability weights (Rx1–Rx3).

Effectiveness data

We based epidemiological data on the WHO Global Burden of Disease (GBD) study, applied to the population of Peru of 2011 [5, 7, 36]. The impact of treatment in Peru was estimated on the basis of stage specific survival rates (case-fatality) from INEN (2000-2010) and previous WHO-CHOICE analyses [18, 37], whereas the impact of trastuzumab on case fatality was based on the literature (Table 3) [38]. Health state valuations originate from disability weights (DWs) of the GBD study, and we assumed that interventions affect DWs in stage IV only. The DW for stage I is equal to the GDB estimate, while for other stages the GBD long term sequel (0,09) was adjusted according to quality of life estimates from the literature [39, 40]. The current stage distribution of women presenting with breast cancer in Peru was derived from INEN (2007-2011) [12], and the impact of the various screening interventions on this stage distribution was estimated on the basis of a model following Duffy et al. by using proportional detection rates [41]. We applied a stage shift from developing countries [17] to the Dutch screening program [42], and corrected this shift for locally relevant attendance rates (72%) and the Peruvian epidemiology and demography. The age specific sensitivity of tests and sojourn times (CBE sojourn times are two-third that of mammography) were based on the literature [41-43]. The effectiveness of the awareness raising interventions are based on a study from Malaysia [28] while we assumed a twofold effect on stage distribution when applying a mass media campaign.

Cost data

Following standardized WHO-CHOICE methodology on CEA, we used an ingredients approach for our costing analysis, in which prices and quantities are separately reported. We distinguished patient-level and program-level costs, and to estimate the total patient costs of interventions we multiplied the unit costs of patient services with the number of patients requiring these services.

Unit costs of patient services were based on the principles of micro-costing, including detailed resource utilization patterns and prices for each procedure (Table S1, Table 4). INEN provided these unit cost to a great level of detail, except for the cost of facilities (buildings, rooms) and the cost for the transportation of drugs and supplies. We derived the transportation multipliers, the size, price and annualization factors for facilities, from a standard WHO-CHOICE database and applied them to each eligible item [20].

We estimated the costs for the FNA intervention through a patient management scheme from the international literature, as this data was not yet available in Peru [33]. We then used average weighted resource patterns for FNA, based on observational studies from different countries [44-49], and assumed similar final outcomes for both CBE screening with upfront FNA and usual CBE screening (Figure S1).

Program-level costs capture management, administrative, media and law-enforcement costs, and costs for training of healthcare personnel. These costs were based on estimates from WHO-CHOICE and from Peruvian program managers (INEN). Media and operating costs (i.e. prices for broadcasting, flyers, and posters) were based on local inventories of prices, also provided by INEN.

For all interventions, we also included costs of diagnostic tests for women presenting with initial symptoms without breast cancer (true-negatives), and assumed the ratio of tested negatives vs. tested positives to be 16.4:1 in non-screened populations and 21.5:1 in screened populations [50, 51]. Single treatment scenarios also include the costs of diagnosing all other stages, and regarding screening interventions, we included costs for evaluating false positives [52].

All costs were estimated in 2012 Peruvian Soles and converted to U.S. dollars (US$) using the 2012 exchange rate (1US$ = 2,603SOL). Both health effects (DALYs) and costs (US$) were discounted at an annual rate of 3%.

Table 3. *Case fatality rates, disability weights and stage distribution used for intervention combinations in Peru*

	Case fatality rates*				Disability weights**				Stage distribution***			
	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	% in stage I	% in stage II	% in stage III	% in stage IV
Untreated	0.021	0.065	0.156	0.311	0.086	0.097	0.104	0.375	7.0%	36.4%	43.5%	13.0%
Treatment only	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	7.0%	36.4%	43.5%	13.0%
Treatment only + Trastuzumab in all HER2 positives	0.006	0.038	0.086	0.247	0.086	0.097	0.104	0.154	7.0%	36.4%	43.5%	13.0%
Current country specific situation (50% coverage), annual opportunistic screening (15%) and free consultation (30%)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.153	7.0%	36.4%	43.5%	13.0%
Basic Palliative Care (BPC)	0.006	0.040	0.093	0.275				0.0153				13.0%
Extended Palliative Care (EPC)	0.006	0.040	0.093	0.275				0.0152				13.0%
Basic Awareness Raising (BAR)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	10.2%	20.1%	44.8%	24.8%
Mass media Awareness Raising (MAR)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	21.1%	41.5%	24.1%	13.3%
Annual CBE screening (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	29.2%-15.8%	31.2%-16.9%	30.4%-51.5%	9.3%-15.8%
Biennial CBE screening (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	26.9%-14.0%	28.8%-14.9%	33.9%-54.4%	10.4%-16.7%
Triennial CBE screening (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	25.4%-12.8%	27.2%-13.7%	36.3%-56.2%	11.1%-17.2%
Annual mammography screening FIXED 60% (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	26.2%-19.7%	29.7%-22.7%	33.6%-43.9%	10.5%-13.7%
Biennial mammography screening FIXED 60% (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	25.7%-19.0%	29.1%-22.0%	34.4%-44.9%	10.8%-14.0%
Triennial mammography screening FIXED 60% (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	25.2%-18.6%	28.6%-21.5%	35.1%-45.7%	11.0%-14.3%
Annual mammography screening FIXED/MOBILE (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	37.4%-26.5%	40.0%-28.4%	17.3%-34.5%	5.3%-10.6%
Biennial mammography screening FIXED/MOBILE (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	36.5%-25.4%	39.0%-27.2%	18.8%-36.2%	5.7%-11.1%

	Case fatality rates*				Disability weights**				Stage distribution***			
	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	% in stage I	% in stage II	% in stage III	% in stage IV
Triennial mammography screening FIXED/MOBILE (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	35.8%-24.6%	38.3%-26.4%	19.9%-37.5%	6.1%-11.5%
Annual CBE/mammography screening MIXED (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	33.6%-22.3%	36.0%-23.8%	23.3%-41.3%	7.1%-12.6%
Biennial CBE/mammography screening MIXED (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275					32.1%-20.9%	34.3%-22.3%	25.7%-43.5%	7.9%-13.3%
Triennial CBE/mammography screening MIXED (age 40-69/40-64/45-64/45-69/50-69/50-64)	0.006	0.040	0.093	0.275	0.086	0.097	0.104	0.154	31.0%-19.9%	33.2%-21.3%	27.4%-45.0%	8.4%-13.8%

Current country specific situation: Current situation in Peru with treatment coverage of 50%, annual opportunistic screening (15%) and free preventive consultations (30%)[12].

** Derived from Bland et al. and stage I and II corrected for the addition of chemotherapy [37]. For trastuzumab CFs were multiplied with 0.66 [38], for eligible patients (eligibility = 12.7% stage I, 12.07%, stage II, 22.0%, stage III, 30.4% stage IV) [53].*

***The DW for stage I is equal to the GDB estimate, while for other stages the GBD long term sequel (0,09) was adjusted according to utilities from the literature [7,32,33] and corrected for relapse to stage IV. Relapse rates were derived from Adjuvant Online [54].*

**** Present stage distribution is based on INEN public sector [12]. Effects of MAR derived from Devi et al [28]. Effects of screening interventions were based on stage shifts from baseline [17] to the stage distribution in The Netherlands[42] . Stage shifts were adapted by calculating relative differences in detection rates between The Netherlands and Peru [41]. Calculations included age specific incidence, prevalence [7], sojourn time [41], sensitivity [43] and attendance rates (72% in Peru)*

Table 4. *Average utilization of main diagnostic and treatment services and unit costs per patient*

Procedure	Ingredients	Stage I	Stage II	Stage III	Stage IV	Palliative (SPC)†	Unit cost per patient (US$)
Initial diagnosis and evaluation during treatment	Medical consultation	2	2	2	2		6.22
	Core biopsy procedure	1	1	1	1		45.02
	Specimen examination	1	1	1	1		9.76
	Bilateral Mammography	1	1	1	1		14.24
	Echo of breast	1	1	1	1		6.20
	Echo of abdominal/pelvic area	1	1	1	1		10.49
	Liver function tests	1	1	1	1		2.07
	Chest X-ray	1	1	1	1		6.79
	Bone scan	1	1	1	1		46.01
	CT of chest	1	1	1	1		96.37
	CT of abdominal/pelvic area	1	1	1	1		115.50
	Multidisciplinary consult	1	1	1	1		100.90

Procedure	Ingredients	Stage I	Stage II	Stage III	Stage IV	Palliative (SPC)†	Unit cost per patient (US$)
Treatment	Pre-operative tests	1	1	1	-		86.57
	Surgical risk analysis	1	1	1	-		20.18
	Surgery	1 (lumpectomy)	1 (lumpectomy /modified radical mastectomy)	1 (modified radical mastectomy)	-		835.88 / 951.77
	Radiotherapy consult	1	1	1	1		7.64
	Radiotherapy planning & first administration*	1	1	1	1		224.20
	Radiotherapy session administration*	32	29.6	24	12		23.36
	AC regimen**	-	4	4	4		104.00
	Taxol regimen**	-	12	4	4		134.47
	Hepatic tests	-	12	12	12		22.14
	Renal tests	-	12	12	12		39.38
	Coagulation tests	-	12	12	12		115.40
	CT	-	2	4	4		115.50
	Bone scan	-	2	2	2		46.01
	% receiving endocrine treatment***	1680	1680	336	336		0.18
	% receiving pain medication					1	9136.87
	% receiving emetics					1	1903.52

** Radiotherapy generally includes a dose of 50 Gy given in 10-35 fractions or boosts on an outpatient basis.*

*** The (neo) adjuvant chemotherapy combination regimen consists of AC-Taxol: AC given 3-weekly for 4 cycles followed by paclitaxel given weekly for 12 weeks or 4 weeks.*

**** Endocrine therapy consists of 20 mg. tamoxifen per day for 5 years.*

† Palliative care is only applied to stage IV patients. Standard Palliative Care (SPC) does not include home based visits. Medication includes Tramadol 50 ml, Morphine 0.02 mg, Fentanyl 50 mg, Parecoxib 40 mg, Triamcinolone 50 mg, Diazepam, Lidocaine, epidural injections, Omeprazol 40 mg, Haloperidol 5mg, Levosulpiride 25mg.

Cost-effectiveness analysis

The average cost effectiveness ratio (ACER) for each intervention is calculated by dividing the total costs of an intervention by its corresponding effects, relative to the comparator situation of no intervention.

In addition to these ACERs, incremental cost effectiveness ratios (ICERs) are reported for the successive set of interventions that can be purchased at expanding levels of resource availability, starting with the intervention with the lowest cost per DALY averted, then moving to the next most cost-effective intervention. The order in which interventions can be selected according to their ICER is called an expansion path, and only interventions that are both more effective and less costly than other (combinations of) interventions are considered on this expansion path. The incremental cost-effectiveness ratios (ICERs) for those interventions are calculated by dividing the incremental costs by the incremental health effects.

CEA results should be furthermore interpreted according to a defined set of cost-effectiveness thresholds. WHO-CHOICE denotes an intervention as "cost-effective" if it produces a healthy year of life for less than three times the gross domestic product (GDP) per capita, and as "very cost-effective" if it produces a healthy year of life for less than the GDP per capita (human capital approach) [55]. In Peru, this means that interventions that cost less than $4,608 per DALY averted can be considered very cost-effective, and interventions that cost between $4,608 and $12,204 can be considered as cost-effective.

Sensitivity Analysis

We performed a deterministic sensitivity analysis to assess the robustness of the results to potential changes in key assumptions regarding the model parameters. Based also on the results of previous sensitivity analyses [16-18], the baseline case fatality rates and DWs were varied +/- 25% and we used other sources for Peru's current case fatality rates [12] and current stage distribution [56]. The effect of awareness raising interventions was reduced by 25%, and we lowered attendance rates of screening interventions and the sensitivity of CBE and mammography tests (-25%). Regarding costs, we varied the transportation multipliers (+/- 25%), and varied the unit costs of CBE and mammography (+/- 25%) as well as the costs for FNA (+/- 25%).

Results

A total of 94 single and combined intervention strategies were assessed and their annual cost, effects, and cost-effectiveness are provided in Table S2 and shown graphically in Figure 2. The annual treatment costs for breast cancer stages I to IV, vary between 7.1 million (treatment of stage I) and 23.0 million US$ (treatment of stage II). Treatment of all stages costs more than $58 million (95% coverage) and expanding this by providing trastuzumab in all stages costs an extra $25 million ($83.8 million in total), while the additional cost for providing trastuzumab only in stage I&II is about $7 million ($65.4 million in total). The additional costs for providing basic or extensive palliative are $1.2 million and $1.6 million ($44.4 and $59.5 million in total) respectively, whereas awareness raising interventions cost $59.8 million (BAR) and $56.0 million (MAR).

The costs of screening interventions generally increase with the screening frequency, e.g. in age groups 40 to 69, the costs are $74.3 to $101.5 million for annual screening strategies and $63.4 to $71.4 for triennial screening strategies. Furthermore, when age group 40 to 45 is included in the screening strategy or annual screening frequencies are applied, costs increase relatively more as compared to age group 65 to 69 and triennial screening frequencies. Screening costs also increase when a mobile screening component is applied, i.e. the costs per mammogram or CBE with a mobile unit are about 20% higher.

The upfront FNA component reduces the costs of CBE screening (as compared to the usual CBE screening strategy) by an estimated $3.48 per women diagnosed (Figure S1). As a result, CBE screening interventions combined with upfront FNA have slightly lower patient costs but higher program and training costs.

In the individual stage I to IV treatment interventions the annual number of DALYs averted vary between 451 (stage IV) and 2,900 (stage II). Jointly these interventions can avert 6,757 DALYs. The addition of trastuzumab to eligible women in stage I&II only averts 313 extra DALYs (a total of 7,080 DALYs), whereas providing trastuzumab to eligible women in all stages can avert 1128 extra DALYs (a total of 7,895 DALYs). The addition of palliative care, both basic (BPC) and extended (EPC), only adds very few DALYs. Awareness raising interventions, combined with treatment of all stages and standard palliative care, avert between 5,306 (BAR) and 12,115 DALYs (MAR).

The various screening intervention combinations avert between 6,000 and 18,000 DALYs, generally much more than treatment interventions only. By increasing screening frequencies and by widening age groups, screening interventions can avert more DALYs. With regards to the age group of screening, including the oldest age group (65-69) seems to avert relatively more DALYs as compared to including the youngest age group (40-45). Annual screening through fixed (urban) and mobile (non-urban) mammography units has the most health impact, and can avert more than 18,000 DALYs when applied in age group 40 to 69 and combined with EPC.

Average cost-effectiveness ratios (ACERs) of the individual treatment interventions range between $5,406 (stage I treatment) and $48,5676 (stage IV treatment) per DALY averted. Treatment of all stages costs $8,605 per DALY averted costs around $10,000 per DALY averted when trastuzumab is added. Palliative care interventions costs $8,782 (BPC) and $8,832 per DALY averted (EPC).

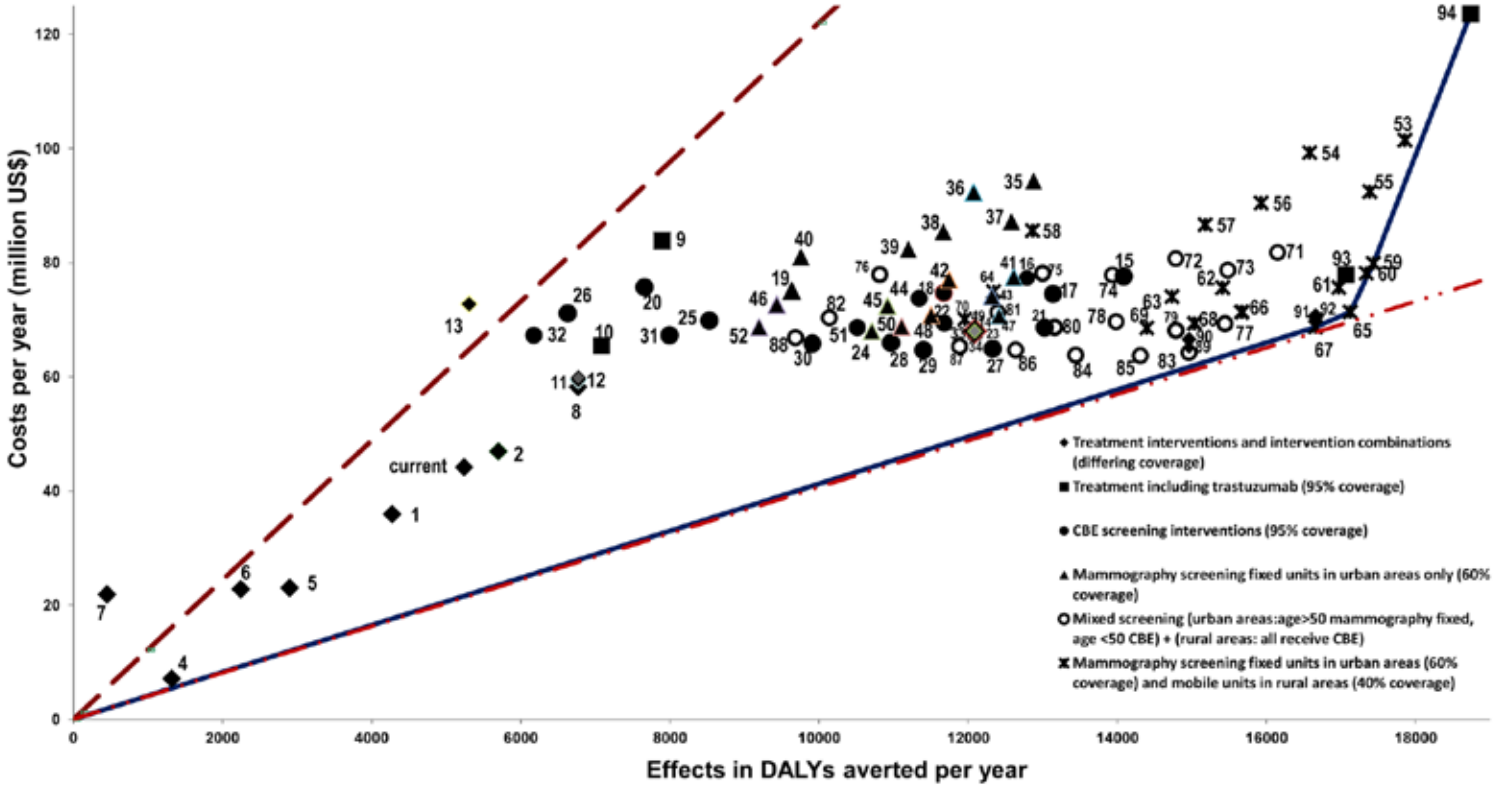
With regards to current breast cancer program in Peru, the ACER of this scenario (scenario #3) is $8,426 per DALY averted. The ACER of mass media awareness raising (MAR) is $5,650 per DALY, yet, basic awareness raising (BAR) costs $13,713 per DALY.

Screening intervention combinations have ACERs ranging from $4,125 to $10,939 per DALY. The most cost-effective screening intervention in our analysis is triennial fixed mammography screening (age 45-69) in urban areas combined with mobile mammography screening (age 45-69) in non-urban areas, which costs $4,125 per DALY averted.

Figure 2 shows the cost-effectiveness thresholds of three times ($12,204) and one time ($4,608) the Peruvian GDP per capita per DALY averted (dotted lines). This figure and Table 5 also show the expansion path for breast cancer control, i.e. the order in which interventions should be implemented at different levels of resource availability on the basis of incremental cost-effectiveness ratio (ICER). This path shows that triennial fixed mammography screening (age 45-69) in urban areas combined with mobile mammography screening (age 45-69) in non-urban areas is the optimal choice ($4,125 per DALY averted, scenario #67), followed by triennial fixed mammography screening (age 40-69) in urban areas combined with mobile mammography screening (age 40-69) in non-urban (ICER of $5,659 per DALY averted, scenario #65). After that, the next best intervention that follows from this expansion path is biennial mammography screening (40-69 years) with fixed and mobile units (ICER $27,477 per DALY, scenario #59). These screening interventions are all combined with treatment of all stages and standard palliative care (SPC). Eventually, annual fixed and mobile screening combined with extended palliative care and trastuzumab (scenario #94) is the most extensive intervention with an ICER of $87,243 per DALY averted.

Note that of the aforementioned interventions, the ICERs of only 2 interventions (scenario #67 and #65) are beneath the proposed cost-effectiveness thresholds. Therefore, strictly interpreted, they are the only candidates for implementation in Peru according to the rules of allocative efficiency. Additionally, other interventions (scenarios #4, #53, #55, #60, #83, #85, #90-#93) are not on the expansion path (i.e. dominated) and should therefore not be considered as well. However, as these small differences in ICERs are likely not relevant at the policy level, we nevertheless consider interventions on - and close to - the expansion path as potential candidates for implementation in Peru (Table 5).

Figure 2. *Cost-effectiveness frontier*



*Cost-effectiveness of breast cancer interventions and expansion path according to ICER (Incremental cost-effectiveness ratio). Dotted lines represent the cost-effectiveness threshold of 3*GDP/capita/DALY averted (12.204 US$/DALY) and 1* GDP/capita/DALY (4.068 US$/DALY).*

Table 5. *Recommended interventions according to their incremental cost-effectiveness ratio (ICER), position in expansion path and budget impact*

Scenario number (#)	Intervention scenarios	Coverage level (%)	Patients per year	Annual treatment costs**	Annual program costs**	Annual training costs**	Annual total costs**	Cost per patient a year**	DALYs averted a year***	DALYs averted per patient a year***	ACER	ICER
4	Stage I treatment & relapse only	95%	1,602	6,582,278	515,816	29,227	7,127,321	4,449	1,318	0,82	5,406	Dominated
85	Stage I to IV treatment with triennial MIXED screening: URBAN (45-49 CBE) (50-69 MM FIXED) 60%/ RURAL (CBE 45-69) 40%*	95%	4,402	53,035,136	10,396,581	276,684	63,708,401	14,473	14,308	3,25	4,453	Dominated
83	Stage I to IV treatment with triennial MIXED screening: URBAN (40-49 CBE) (50-69 MM FIXED) 60%/ RURAL (CBE 40-69) 40%*	95%	4,402	53,577,050	10,396,581	276,684	64,250,315	14,596	14,959	3,40	4,295	Dominated
89	Stage I to IV treatment with most efficient triennial MIXED: URBAN (40-49 CBE) (50-69 MM FIXED) 60%/ RURAL (CBE 40-69) 40%*+ FNA*	95%	4,402	53,557,982	11,208,251	292,272	65,058,506	14,779	14,959	3,40	4,349	Dominated
90	Stage I to IV treatment with most efficient triennial MIXED: URBAN (40-49 CBE) (50-69 MM FIXED) 60%/ RURAL (CBE 40-69) 40%* + FNA + BPC	95%	4,402	53,539,583	12,511,232	518,783	66,569,598	15,123	14,961	3,40	4,450	Dominated
67	Stage I to IV treatment with triennial mammography screening (45-69 years) FIXED 60%/MOBILE 40%*	95%	4,402	54,944,080	13,423,175	350,727	68,717,982	15,611	16,657	3,78	4,125	4,125
91	Stage I to IV treatment with most efficient triennial FIXED/MOBILE screening strategy (FIXED/ MOBILE, 45-69) + BPC	95%	4,402	54,804,394	14,726,156	577,237	70,107,788	15,926	16,658	3,78	4,209	Dominated

Scenario number (#)	Intervention scenarios	Coverage level (%)	Patients per year	Annual treatment costs**	Annual program costs**	Annual training costs**	Annual total costs**	Cost per patient a year**	DALYs averted a year***	DALYs averted per patient a year***	ACER	ICER
65	Stage I to IV treatment with triennial mammography screening (40-69 years) FIXED 60%/MOBILE 40%*	95%	4,402	57,581,446	13,423,175	350,727	71,355,347	16,210	17,123	3,89	4,167	5,659
60	Stage I to IV treatment with biennial mammography screening (40-64 years) FIXED 60%/MOBILE 40%*	95%	4,402	62,065,226	15,710,263	370,211	78,145,701	17,752	17,338	3,94	4,507	Dominated†
59	Stage I to IV treatment with biennial mammography screening (40-69 years) FIXED 60%/MOBILE 40%*	95%	4,402	63,804,007	15,710,263	370,211	79,884,482	18,147	17,433	3,96	4,582	27,477†
55	Stage I to IV treatment with annual mammography screening (45-69 years) FIXED 60%/MOBILE 40%*	95%	4,402	74,070,789	17,997,352	389,696	92,457,837	21,004	17,385	3,95	5,318	Dominated†
53	Stage I to IV treatment with annual mammography screening (40-69 years) FIXED 60%/MOBILE 40%*	95%	4,402	83,070,430	17,997,352	389,696	101,457,478	23,048	17,857	4,06	5,682	Dominated†
94	Stage I to IV treatment with most expensive screening strategy (annual, FIXED60%/MOBILE40%, 40-69) + EPC + trastuzumab (all stages)	95%	4,402	103,306,498	19,638,424	625,949	123,570,871	28,072	18,737	4,26	6,595	87,243†

ICER = Incremental cost effectiveness ratio, ratio of additional cost per additional life-year saved when next intervention is added to a mix (additional US$ per additional DALY saved;. ACER = Average cost-effectiveness ratio compared to the do nothing-scenario (US$ per DALY averted); MIXED screening: combines both CBE screening and mammography screening elements in the screening program;. URBAN: program specified for urban population, covers about 60% of the total population; RURAL: program specified for rural population, covers about 40% of the total population; CBE: clinical breast examination screening; MM: mammography screening; FIXED: screening program based on fixed mammography units; MOBILE: screening program based on mobile screening unit; FNA: upfront fine needle aspiration program; BPC: basic palliatice care program; EPC: extende palliative care program.

** These scenarios include Standard Palliative Care (SPC)*

*** In 2012 US$ (1 SOL = 0,384 US$)*

**** DALYs, disability-adjusted life-years (age weighted, 3% discounted) . DALYs are averted over a 100 year period but attributed to the implementation period of 10 years.*

† These interventions have ICERs higher than the 3 times GDP per capita per DALY threshold and can, strictly speaking, not be considered cost-effective.

Sensitivity Analysis

Sensitivity analysis showed that our model is most sensitive to alternative assumptions on screening attendance and the sensitivity of screening devices. Varying the case fatality rates and current stage distribution also impacts our results, whereas alternative assumptions on unit costs for FNA or mammography, transportation multipliers or DW's have less impact (Table S3). Lowering screening attendance from 72% to 54% (-25%) would increase the ACERs with about 26%, while lower test sensitivities of CBE and mammography screens (-25%) would increase the ACERs with about 24%. If higher case-fatality rates were assumed (+25%), representing poorer survival, the ACERs of the interventions in table S3 would increase about 22%. Lower case-fatality rates would result in a 15% decrease of these ACERs. Increased intervention costs due to respectively higher unit costs of FNA, mammograms and transportation multipliers (+25%) increase the ACERs between 0% and 9%.

Discussion

We have quantified the health effects, costs, and cost-effectiveness of a broad range of interventions for breast cancer control in Peru. The results were obtained by means of a dynamic population model, using consistent demographic and epidemiological data of the populations, allowing general comparisons of the costs and effects of the interventions studied.

Our results provide important information on strategies for breast cancer control in Peru and suggest that the current situation in Peru could be improved through implementation of triennial or biennial mammography screening strategies, combined with treatment of all strategies and standard palliative care. These strategies seem the most cost-effective in Peru, and costs between $68 and $80 million per year. Probably also cost-effective, but less expensive, are triennial screening strategies through combining mammography and CBE screening. These strategies, combined with or without basic palliative care or upfront FNA, cost between $64 and $66 million per year. Annual screening strategies come with higher cost to the healthcare system and with relatively lower effects compared to tri- or biennial screening, and are therefore not recommended from an economic perspective.

Of the abovementioned interventions, only triennial mammography screening strategies can be labeled cost-effective (scenario #67 and #65). However, considering the uncertainty on the effectiveness of these interventions, and considering the inappropriateness to use this threshold as the sole criterion for choosing interventions at the policy level, we suggest considering all the interventions near the expansion path for planning (long term) strategies (Table 5). Besides the efficiency aspects of the studied interventions, we believe the choice of intervention should also relate to other aspects of the health system such as budget impact, equity and feasibility. These aspects are discussed below.

First, compared to mammography screening, CBE screening with upfront FNA implies a simpler and technically less demanding approach at the primary healthcare level. Although the total costs of adding the upfront FNA component are slightly higher (about $240,000 per year), patient costs can be slightly reduced due to the lower costs of the FNA strategy ($3.48 saved per diagnosis) and the implementation of this intervention has been demonstrated in a very rural area [25]. This intervention, which includes an awareness raising of signs and symptoms component, could be recommended above usual CBE screening strategies in Peru for feasibility reasons, especially in rural areas.

Second, although treatment interventions are - on themselves - not economically attractive, treatment is an integral component of the continuum of care and essential to be scaled up if any screening intervention is implemented. Only 60% of the Peruvian population is currently insured, creating high barriers to accessing care for many Peruvians. Besides treatment interventions, awareness raising of signs and symptoms (particularly in areas where breast cancer is diagnosed in late stages) is imperative for early detection [57]. Also, if any form of early detection or screening is implemented, patients need to be referred through to a comprehensive system with low social and financial barriers. This could partly be managed by reimbursing patients and their families for travel and accommodation. Efforts to reach universal coverage should therefore continue and a gradual increase in coverage of current treatment services, along with improvements of referral systems should first - or simultaneously - be established in Peru.

Third, stage IV treatment only (including standard palliative care (SPC)) is the least economically attractive intervention (ACER of $48,576 per DALY), and generally palliative care cannot be recommended from an economic perspective. If management of stage IV patients entails home based visits (BPC), patient costs slightly decrease due to a reduction of hospitalization days. However, the extra training and program cost for organizing this palliative service model outweigh these savings and BPC is not cost-effective either. Nevertheless, this intervention costs only slightly more than the current SPC ($1.2 million more) and allows patients to decease at home, where family and friends are able to support and spend their last moments with the patient. For this reason, and regarding the many patients in advanced stages currently, it could be meaningful to provide basic palliative care in Peru.

Fourth, the addition of trastuzumab to all eligible patients (about 15% of all patients), is less economically attractive than treatment of all stages (ACER of $10,620 vs. ACER of $8,605 per DALY). Moreover, it comes with an additional cost of over $25 million ($83.8 million in total) - almost 45% higher than the budget for treatment of all stages. If trastuzumab is given only to eligible patients in stage I and II, this ACER is lower ($9,247 per DALY) and the additional costs are about 12% higher ($65.5 million in total). This intervention should therefore be preferred if trastuzumab is added as a therapeutic option for breast cancer control. The addition of trastuzumab to all eligible patients is not recommended for Peru.

Fifth, breast cancer screening highly depends on the availability of human resources, facilities and devices for proper diagnosis and treatment. It is necessary to secure adequate infrastructure, equipment and human resources before any screening activities can commence. In addition, as the current health system in Peru is fragmented and in a decentralization process, it seems very difficult to achieve nationwide, organized screening. If screening is provided by competitive public and private actors, all with their own target populations in the same areas, we recommend either law enforcement and strong leadership to negotiate a plan with all these actors, or installing a separate public operation that could provide the entire screening programme. Attendance rates are perhaps equally important for both the success of screening and the equitable distribution of its health outcomes. In this, appropriate education and information is essential and although most screening studies show positive results on stage distribution in developing countries [29, 58, 59], these interventions can easily fail when education and information are neglected. Screening or early detection communications strategies should also include clear messages on the benefits and harms of the different early detection modalities [57]. Our sensitivity analysis furthermore showed that if attendance rates reduce from 72% to 54%, the ACERs of screening interventions increase with 26%.
We therefore recommend a thorough evaluation of Peru's current screening activities, so these barriers become more transparent and future screening programs can better guarantee adequate attendance and equal access.

Sixth, mobile screening units are generally more accessible in non-urban areas as opposed to fixed mammography units and therefore more effective. Mobile screening could also lead to a more equal distribution of health outcomes and could therefore be considered if screening is implemented. However, the costs for reaching out to the non-urban areas (30%-40% of total population) by mobile units are high as the cost of each screen increases with at least 20%. A combination of CBE screening and mammography screening (mixed screening) seems a cost-effective alternative with lower budget impact, and less complex to implement in non-urban areas compared to mobile mammography screening. Hence, we generally recommend Peru to consider a mixed screening strategy (CBE screening below 50 and mammography screening in women older than 50 for urban areas, and CBE screening in all ages for non-urban areas) for feasibility and budgetary reasons.

Seventh, and in general, the current budget for controlling priority cancers in Peru (colo-rectal, stomach, cervical, breast, prostate, lymphomas, leukemia) has been increased to over $25 million for 2012 [11]. Despite this impetus, the full implementation of the broad range of breast cancer interventions already requires more budget. Treatment of all patients with breast cancer would costs around $58 million per year, and screening will at least cost another $5 million per year. Moreover, the budget for (breast) cancer control also faces competition with other healthcare interventions. International literature suggests that interventions for communicable diseases and preventive interventions for non-communicable diseases are economically more attractive compared to breast cancer interventions [20, 60, 61].

With regards to the economic attractiveness of screening interventions for other non-communicable diseases, breast cancer screening seems to compare worse to cervical screening but better compared to colorectal screening [16]. Yet, these international estimates should be carefully interpreted for national level decision making. Given these budgetary constraints, the MoH in Peru could decide to implement less expensive interventions such as CBE screening, mass-media awareness raising, or treatment only. This would however introduce an inefficient use of resources and instead we suggest to gradually expand the recommended screening interventions, starting at lower -more affordable- coverage levels. The MoH in Peru could for example first increase treatment coverage and select an urban area to demonstrate triennial CBE and mammography screening in currently targeted women (45-64 years). In a non-urban area, awareness raising and CBE screening could first be initiated and combined with upfront FNA.

Once a reasonable increase in coverage is reached, the program could expand to screening women 45 to 69 years, or 40-69 years old, possibly by mobile units providing both mammography and CBE. These mobile units could be shared for the screening and early detection activities of the other priority diseases. The gradual expansion will give extra time to train the required human resources and to negotiate more budget for infrastructure and equipment.

Our study has a number of limitations. First, a national cancer registry in Peru is not yet available and local data on breast cancer epidemiology and patient resource patterns were derived from different sources. Breast cancer treatment practices probably differ between the many public and private institutions. Since our data was mostly based on composite hospital data from the urban, public sector, our results may not be representative for the whole country. These limitations indicate the need to start a national cancer registry in Peru. Second, evidence on the effectiveness of awareness raising, CBE and mammography screening in Peru and many other countries is absent. To arrive at Peruvian estimates we used a model approach that has previously been applied in a range of other studies and was also considered credible by the expert panel in our study. Also, our sensitivity analysis shows that using alternative assumptions on case fatality rates, attendance rates or the sensitivity of screening devices lead to significant differences in cost-effectiveness. A combined effect of these factors could change the cost-effectiveness of the interventions under study further. However, as these factors have a similar impact on all interventions under study, it is unlikely that this combined effect would change our study conclusions. Despite these limitations, the results of our model show similarities with results from other models [59, 62, 63]. Third, as information on the patient resource patterns of the upfront FNA strategy was limited in Peru, we assumed similar final outcomes for both CBE screening with upfront FNA and the usual CBE screening strategy (i.e. the number benign or malignant outcomes in both arms in Figure S1).However, FNA could also cause structural distortions that may render further imaging accuracy. Fourth, in the absence of reliable data and following the health care perspective of the Peruvian MoH, we did not include travel costs or productivity losses of patients seeking or undergoing care.

Including these cost would have probably led to increased cost generally, and particularly for women with advanced stage breast cancer [64, 65]. WHO-CHOICE analyses aim to provide broad indications of cost-effectiveness on a range of interventions to inform general policy discussions rather than to deliver very precise estimates on a specific intervention and the above limitations are a manifestation of this.

Conclusions

In summary, taking in consideration cost-effectiveness and other factors, our analysis suggests that CBE screening with upfront FNA in non-urban settings (age 40-69), combined with both CBE and fixed mammography screening in urban settings (age 40-69), could be a preliminary, cost-effective and feasible option for Peru. A combination of fixed and mobile mammography screening, due to its high budget impact and the challenging implementation characteristics, should perhaps be preferred on the long term when the economic and health system conditions improve. However, whichever screening modality is used, awareness raising of signs and symptoms, cancer diagnosis, cancer treatment and basic palliative care services should be improved simultaneously and barriers to early detection and breast cancer care along the continuum should also be explored and dissolved. As population based screening programs are very complex and resource intensive, particularly mammography screening, we suggest Peru to focus initially on triennial screening in women currently targeted (age 45-64) in urban and non-urban demonstration areas and gradually expand to the proposed program. Annual screening strategies, late stage treatment and trastuzumab therapy are generally not economically attractive.

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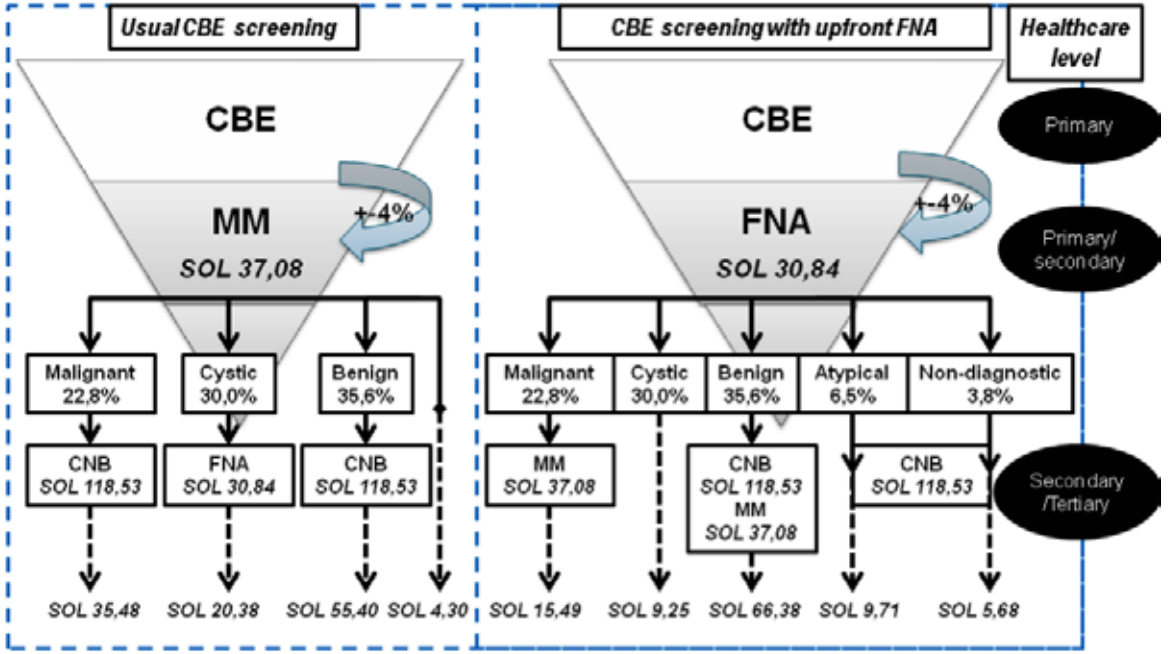
Supporting information

Figure S1. *Comparison of usual CBE screening strategy and CBE screening with upfront FNA, and level of execution.*



CBE screening with upfront FNA (fine needle aspiration): after a positive CBE screen (about 4% of the CBE screened population) women receive FNA. Depending on the FNA test results, mammography (MM) or core needle biopsy (CNB) is performed as part of the triple test (physical examination, mammography, needle biopsy) for final breast cancer diagnosis.

Table S1. *Example of micro costing study results (i.e. core biopsy), and their modifications in Peru*

CORE BIOPSY MICRO COSTING							Multiplier drugs/ goods*
HUMAN RESOURCES		Time (min)		HR wage	HR per min.	Cost per procedure	
Medical doctor		10		4,500.00	0.50000	5.00000	
Nursing assistent		10		1,800.00	0.20000	2.00000	
Total						*7.00000*	
REUSABLE ITEMS		Time (min)	Buying price	Useful Life	Depreciation per min.	Cost per procedure	
Trolley		10	500.00	10	0.00010	0.00096	
Metal stretcher		10	968.00	10	0.00019	0.00187	
Total						*0.00283*	
DISPOSABLE ITEMS	Presentation	Buying price	Unit definition	quantity used	Price per unit	Cost per procedure	
1. Activity: Skin Cleaning							
Gauze (x 2 und)			Pack	3	0.45442	1.36325	
Alcohol			Ml	1	0.02079	0.02079	
Formaldehyde			Ml	5	0.02140	0.10700	
Plaster			Cm	20	0.01067	0.21333	
2. Activity: Procedure							
5cc disposable syringe. C / A 21x1 1/2"			Piece	1	0.13000	0.13000	
Disposable needle 25X5/8X100			Piece	1	0.06800	0.06800	
21x1 disposable needle 1/2X100			Piece	1	0.06800	0.06800	
Biopsy Needle 14 x 10			Piece	1	90.25000	90.25000	
25.10cm x 24.5cm Paper Towel x 175 sheets	175	6.46	Sheet	4	0.03691	0.14766	
Germicidal Soap Liquid x 800ml	800	11.00	Ml	6	0.01375	0.08250	
Total						*92.45053*	*106.32366*

CORE BIOPSY MICRO COSTING							Multiplier drugs/ goods*
FACILITIES**	Time (min)	Size	Useful Life	Replacement costs per m2	cost per m2	Cost per procedure	
Examination / procedure room	12.5	12.5	15	3120	0.17265	0.44962	
DRUGS & MEDICATION	Presentation	Buying price	Unit definition	quantity used	Price per unit	Costs per procedure	
Xilocaine 2%			Fco	1	3.50000	3.50000	
						3.50000	5.20205
TOTAL COSTS						102.95	118.52854

This procedure does not include specimen examination.

** Drug and goods multipliers are derived from WHO-CHOICE database and are used to correct for cost of shipping and transportation. Multipliers are 1,4863 for drugs, and 1,1501 for goods.*

*** Details on facilities also derived from CHOICE database. Annualization (r=3%) is: A= ((1+r)^useful life-1)/(r*(1+r)^useful life). Maintenance costs for facility is 7%, capacity utilization is 240 working days for 8 hours a day [20].*

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5

CHAPTER

Cost-Effectiveness of Breast Cancer Control Strategies in Central America

the cases of Costa Rica and Mexico

The house does not rest upon the ground, but upon a woman

(Mexican proverb)

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Abstract

Objective

This paper reports the most cost-effective policy options to support and improve breast cancer control in Costa Rica and Mexico.

Methods

Total costs and effects of breast cancer interventions were estimated using the health care perspective and WHO-CHOICE methodology. Effects were measured in disability-adjusted life years (DALYs) averted. Costs were assessed in 2009 United States Dollars (US$). To the extent available, analyses were based on locally obtained data.

Results

In Costa Rica, the current strategy of treating breast cancer in stages I to IV at a 80% coverage level seems to be the most cost-effective with an incremental cost-effectiveness ratio (ICER) of US$4,739 per DALY averted. At a coverage level of 95%, biennial clinical breast examination (CBE) screening could improve Costa Rica's population health twofold, and can still be considered very cost-effective (ICER US$5,964/DALY). For Mexico, our results indicate that at 95% coverage a mass-media awareness raising program (MAR) could be the most cost-effective (ICER US$5,021/DALY). If more resources are available in Mexico, biennial mammography screening for women 50-70yrs (ICER US$12,718/DALY), adding trastuzumab (ICER US$13,994/DALY) or screening women 40-70yrs biennially plus trastuzumab (ICER US$17,115/DALY) are less cost-effective options.

Conclusions

We recommend both Costa Rica and Mexico to engage in MAR, CBE or mammography screening programs, depending on their budget. The results of this study should be interpreted with caution however, as the evidence on the intervention effectiveness is uncertain. Also, these programs require several organizational, budgetary and human resources, and the accessibility of breast cancer diagnostic, referral, treatment and palliative care facilities should be improved simultaneously. A gradual implementation of early detection programs should give the respective Ministries of Health the time to negotiate the required budget, train the required human resources and understand possible socioeconomic barriers.

Keywords

Cost-effectiveness analysis; WHO CHOICE; Breast cancer; Costa Rica; Mexico

Introduction

Due to population ageing and changing lifestyles in low-and-middle countries (LMICs), breast cancer incidence rates are increasing [1,2]. Given the organizational and financial constraints faced by the health systems in LMICs the majority of breast cancers are diagnosed at late stages [3]. Accordingly, the majority of breast cancer deaths occur in LMICs [4,5]. The World Health Organization (WHO) therefore states that early detection and implementation of cost-effective interventions should be a priority in LMICs [6]. In an attempt to support LMICs with breast cancer control, the Susan G. Komen for the cure foundation provided a grant to investigate the cost-effectiveness of several breast cancer control interventions in 7 LMICs to a consortium of the WHO, Erasmus University Rotterdam (EUR) and Radboud University Nijmegen Medical Center (RUNMC). Cost-effectiveness analyses may support governments in deciding how to spend scarce resources in health care most efficiently.

In each country, during four phases, the consortium works closely with local authorities and experts in the fields of breast cancer, health economics, epidemiology and public policy. First, a three-day technical workshop is held, where the consortium explains a general cost-effectiveness model based on WHO-CHOICE methodology (described elsewhere [7,8]) which is to be tailored to the country specific situation. In the second phase, lasting approximately six months, local authorities identify and assemble the (local) data required for the cost-effectiveness model. Subsequent in phase three, the cost-effectiveness analyses are carried out. Thereafter, a second workshop is organized. Here the results of the analyses are discussed among representatives of all local institutions involved in breast cancer care and made available for actual policy making by the local health authorities, i.e. the fourth phase. This paper identifies the most cost-effective interventions for breast cancer control in both Costa Rica and Mexico from a health care perspective.

After presenting an overview of the situation regarding breast cancer in both Costa Rica and Mexico, we discuss the methods, data and interventions considered in this study and discuss the results.

Breast cancer in Costa Rica and Mexico

Cancer incidence and mortality rates are rising across Central America [9,10]. In Costa Rica and Mexico breast cancer ranks among the top-five causes of death for women over 25 years old [11]. Between 1995 and 2003, breast cancer incidence increased by 32.3% to a rate of 40.07 per 100,000 women in Costa Rica [12]. In Mexico, breast cancer incidence increased as well and in both countries breast cancer mortality rates have increased since the 1980s [9,13,14]. In Costa Rica 13.14 breast cancer deaths per 100,000 women in 2006, the highest number among malignant neoplasms, are observed. Mortality rates per 100,000 women range from 28.19 in province 'Dota' to 1.23 Guácimo, while in provinces 'Los Chiles, 'La Cruz', and 'Garabito' no breast cancer related deaths were registered [12]. In Mexico mortality rates doubled over the last 20 years.

The average mortality rate per 100,000 women in Mexico stands at 9.9 with regional differences from 13.2 and 11.8 respectively in the Federal District and the north to 9.7 and 7.0 respectively in the center and the south [15]. This increase caused breast cancer to overtake cervical cancer as the most deadly cancer among females in 2006 [14,15]. Where in 1979 1,144 females died from the disease, in 2006 4,497 deaths were registered [15].

Although in Costa Rica and Mexico official recommendations for both breast self-examination (BSE) and mammography screening have existed for over a decade, their coverage levels remain very low and the large majority of breast cancer patients present at the hospital with advanced disease [16-18].

In light of the above, Non-Governmental Organizations (NGOs) and the general public put pressure on governments in Costa Rica and Mexico to improve treatment and early diagnosis through screening [19,20]. Hence, both countries face choices on efficient allocation of scarce resources for breast cancer screening.

Materials and Methods

Methods

General approach

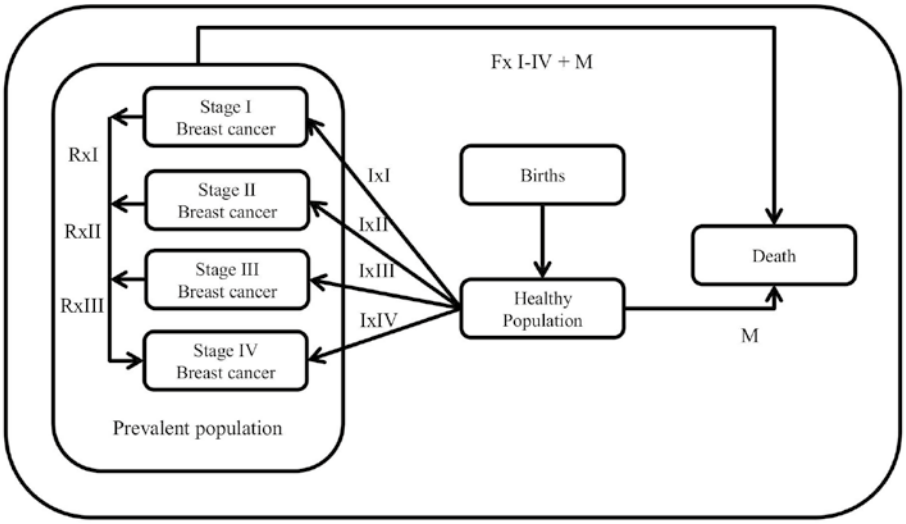
We used the WHO-CHOICE methodology, described in detail elsewhere [7,8], as a basis of our analysis. This approach compares all possible interventions in a specific disease area to a situation where no interventions are implemented. The latter, a counterfactual 'null scenario', acts as a reference to compare the costs and effects of existing and new interventions. An intervention in isolation, or a combination of different interventions, is then implemented for 10 years in a modeled population. However, to include effects that occur after these 10 years, this modeled-population is tracked for 100 years. This approach enables us to make comparisons of the costs and health effects across a wide range of competing interventions, identify differences in relative cost-effectiveness and identify the most efficient mix of interventions to improve population health.

Breast Cancer Model

Costs and health effects are calculated using a state transition population model developed and explained in detail by Groot et al. [7]. Its structure is presented in Figure 1. The model simulates the development of a national population and accounts for births, background mortality and breast cancer epidemiology of a country. It includes a healthy state, a deceased state, and stage I to IV breast cancer states following the classification of the American Joint Committee on Cancer (AJCC) [21]. The effectiveness of each intervention is expressed in changes in disability weights (DWs i.e. health state valuations (HSVs)), case fatality rates (CFs, i.e. improved survival for treatment scenarios), or in more positive stage distributions (in awareness raising and screening interventions).

Since the interventions affect mortality (i.e., CFs) and morbidity (DWs), intervention effectiveness is expressed in disability adjusted life years (DALYs) averted. The difference in the total number of healthy years lived by the population between each scenario and the null-scenario gives the population health gains in DALYs averted.

Figure 1. *Graphical representation of the model showing the relationships between the different health states through the incidence rates of breast cancer (Ix I–Ix4), the different stage specific case fatality rates (Fx I–4), and the background mortality (M)* [7].



Stage specific relapse rates to stage IV were used to correct health state valuations only (Rx I–Rx3).

Zelle et al. [22] improved the published model [7] by correcting HSVs for relapse, assuming that patients could only relapse to stage IV at a constant rate [23].

Interventions

An important element of the overall project is to select a set of appropriate interventions for breast cancer control in LMICs. Therefore, a study group at WHO-CHOICE defined a mix of 11 common and preferable practices in 2009 [22]. Participating countries can combine and adapt these practices to appropriately inform their specific policy questions. For Costa Rica and Mexico focus was placed on the cost-effectiveness of screening & treatment combinations. The most urgent policy questions in both countries concerned the age groups that should be targeted for screening and whether treating Her2/NEU+ patients with Trastuzumab (Herceptin™) was cost-effective. Therefore, the basic awareness raising intervention was excluded and different intervention scenarios, including treatment with Trastuzumab, were added. Combining the 11 common practices with or without Trastuzumab led to a total of 19 scenarios. Input from local policy makers led us to model the current situations of breast cancer control in Costa Rica and Mexico at 80% and 70% geographic coverage levels (i.e. reaching 80%/70% of those people who need services) respectively. In line with WHO-CHOICE methodology all other interventions were evaluated at a geographic coverage level of 95% [8]. An overview of the interventions is listed in table 1.

Table 1. *Definition and classification of individual interventions (coverage)* [22]

Treatment of individual stages	Down-staging interventions [b]	Palliative care [d]
Stage I treatment: lumpectomy with axillary dissection and radiotherapy. Eligible patients receive tamoxifen [a] or chemotherapy [e] [7,23,49].	Basic Awareness Raising (BAR): community nurses training program + opportunistic outreach activities by community nurses to raise breast cancer awareness and educate on breast self-examination techniques (BSE) + enhanced media activities [50].	Basic Palliative Care (BPC): palliative care volunteers training program + home-based visits by volunteers every fortnight + pain treatment through morphine, laxatives and palliative radiotherapy (8 Gy in 1 fraction) for eligible patients [49-51].
Stage II treatment: lumpectomy with axillary dissection and radiotherapy. Eligible patients receive tamoxifen[a] or Chemotherapy [e] [7,23,49].	Mass-media awareness raising (MAR): BAR + mass media campaign [50].	Extended Palliative Care (EPC): BPC apart from community nurses instead of palliative care volunteers, pain treatment strengthened with antidepressants, anti-emetics and zelodronic acid [50-54].
Stage III treatment: modified mastectomy followed by adjuvant chemotherapy [e] and radiotherapy [f]. Eligible patients receive tamoxifen[a] [7,49].	Biennial clinical breast examination (CBE) screening in asymptomatically women aged 40–69 years: community nurses training program + active outreach screening by community nurses +limited media activities [50,55].	
Stage IV treatment: adjuvant Chemotherapy [e] and radiotherapy (10 Gy) + end of life hospitalization. Eligible patients receive total mastectomy and / or tamoxifen [a] [49,56].	Biennial mammography screening in asymptomatic women aged 50–69 years + limited media activities [7].	
Treatment of stage I – IV as listed above plus the addition of Trastuzumab [g] for Her2/NEU+ patients.	Biennial mammography screening in asymptomatic women aged 40–69 years + limited media activities [7].	

[a] Endocrine therapy consists of 20 mg tamoxifen per day for 5 years; [b] Down-staging interventions cause [a] shift in stage distribution and are only modeled in combination with treatment of all stages (I–IV); [c] BAR was excluded as a standalone intervention in Costa Rica and Mexico; [d] Palliative care interventions are only applied to stage IV patients, and substitutes stage IV treatment; [e] The (neo)adjuvant chemotherapy combination regimen consists of 7 cycles of Epirubicin, Fluorouracil and cyclophosphamide (FEC regimen) Given on an outpatient basis; [f] Radiotherapy includes a standard dose of 50 Gy given in 25 fractions of 2 Gy on an outpatient basis; [g] Trastuzumab is given for 8 months.

Data

Effectiveness

A key factor is the stage distribution of patients presenting at the hospital, given the breast cancer stage determines the survival and disability of the breast cancer patients and the effectiveness of each intervention [21].

In Costa Rica we obtained the current stage distribution from Ortiz [24], who studied breast cancer survival in Costa Rica between 2000 and 2003. Demographic data and incidence rates were obtained from the Statistical office of the Costa Rican Ministry of Health (MoH). For the prevalence we used the 2004 Global Burden of Disease estimates [25].

For Mexico, we used the current stage distribution from Knaul et al. [17], who studied 1904 patients that were all treated within the Mexican Social Security Institute (IMSS, its abbreviation in Spanish). Demographic data were obtained from the Mexican National Population Council [26]. For Mexico we obtained incidence rates based on GLOBOCAN 2008 adjusted by group of age considering the distribution from the Mexican Histopathology Registry 2006 [27,28]. For the prevalence in Mexico, as in Costa Rica, we used 2004 Global Burden of Disease estimates [25].

The case fatality rates for the treatment scenarios were based on Groot et al. (stage III & IV) and Zelle et al. (stage I & II), who corrected those from Groot et al. for the use of chemotherapy in stage I and II [7,22]. We take these CF's to represent technical efficiency, representing the maximum amount of DALYs that can be averted based on successful implementation of breast cancer diagnosis, treatment and follow-up. Disability weights were derived from the Global Burden of Disease estimates for long term sequela [25] using quality of life literature [26,27]. For stage I we took the disability estimate of 0.086 [28] and for stage IV we combined the terminal estimate of 0.75 [28] with estimates from quality of life literature [26].

Since screening and awareness interventions as defined in international literature, alter the stage distribution, their effects on the stage distribution at presentation were estimated using the same methods applied by Zelle et al. [22]. Zelle et al. use international study results to estimate the health effects of various screening options and account for the sensitivity of the screening method, attendance rates (80% in both countries), incidence rates and demography in target groups.

Table 2. *Analyzed interventions and the estimates used for the stage were interventions are applied to*

	Case Fatality Rates [a]				Disability Weights [b]				Stage Distribution [c]			
Costa Rica (CR) - Intervention	stage I	stage II	stage III	stage IV	stage I	stage II	stage III	stage IV	% in stage II	% in stage II	% in stage III	% in stage IV
Untreated	0.0207	0.0654	0.1556	0.3112	0.086	0.097	0.104	0.375	14.6%	41.6%	20.4%	23.4%
Stage I treatment	0.0056				0.086				14.6%			
Stage II treatment		0.0393				0.097				41.6%		
Stage III treatment			0.0930				0.104				20.4%	
Stage IV treatment				0.2750				0.154				23.4%
Basic Palliative Care (BPC)				0.2750				0.153				23.4%
Extended Palliative Care (EPC)				0.2750				0.152				23.4%
Current Country Situation	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	14.6%	41.6%	20.4%	23.4%
Mass-media Awareness Raising (MAR)	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	21.1%	41.5%	24.1%	13.3%
Biennial CBE screening (40-69)	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	32.0%	34.3%	25.8%	7.9%
Biennial mammography screening (50-69)	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	35.0%	37.5%	21.1%	6.5%
Biennial mammography screening (40-69)	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	40.0%	42.8%	13.2%	4.0%
With Trastuzumab	0.0050	0.0353	0.0835	0.2470	0.086	0.097	0.104	0.154				

Mexico(MX) - Intervention	stage I	stage II	stage III	stage IV	stage I	stage II	stage III	stage IV	% in stage I	% in stage II	% in stage III	% in stage IV
Untreated	0.0207	0.0654	0.1556	0.3112	0.086	0.097	0.104	0.375	13.8%	39.6%	33.9%	12.7%
Stage I treatment	0.0056				0.086				13.8%			
Stage II treatment		0.0393				0.097				39.6%		
Stage III treatment			0.0930				0.104				33.9%	
Stage IV treatment				0.2750				0.154				12.7%
Basic Palliative Care (BPC)				0.2750				0.153				12.7%
Extended Palliative Care (EPC)				0.2750				0.152				12.7%
Current Country Situation	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	13.8%	39.6%	33.9%	12.7%
Mass-media Awareness Raising (MAR)	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	21.1%	41.5%	24.7%	12.7%[d]
Biennial CBE screening (40-69)	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	30.5%	32.6%	28.3%	8.7%
Biennial mammography screening (50-69)	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	33.9%	36.3%	22.8%	7.0%
Biennial mammography screening (40-69)	0.0056	0.0393	0.0930	0.2750	0.086	0.097	0.104	0.154	39.1%	41.8%	14.6%	4.5%
With Trastuzumab	0.0054	0.0374	0.0865	0.2569	0.086	0.097	0.104	0.154				

[a] Estimates for stages III and IV are from Groot et al. [7] and for stages I and II from Zelle et al [22];The CFs for the untreated patients are from Groot et al. and were corrected based on Bloom et al [57];

[b] Estimates from Zelle et al.[22]; [c] Current stage distribution CR is based on Ortiz [24], MX onKnaul et al.[17], Effects of MAR derived from Devi [50], Effects of screening interventions were based on stage shifts from baseline Groot et al.[7] to the stage distribution USA in Bland et al. [58]. Stage shifts were adapted [b]y calculating relative differences in detection rates between the USA and CR / MX from Duffy & Gabe [59]. Calculations included age-specific incidence (MoH CR & Unidad Analysis Económica MX), prevalence (WHO 2008), sojourn time Duffy & Gabe [59], sensitivity Bobo et al. [60] and attendance rates (75% in the USA vs. 80% in Costa Rica and Mexico); [d] We assumed in Mexico implementing MAR could not lead to a higher proportion of stage IV patients and increase stage III with the difference of 0.6%.

Costs

In line with the WHO-CHOICE approach we distinguished patient, program and training costs, which were calculated by multiplying quantities of applied procedures by their corresponding unit costs. Patient costs were dependent on patient consumption (utilization) of explicit resources (procedures) for diagnosis, treatment, follow-up, early detection and screening.

Although Costa Rica has developed several guidelines for treating breast cancer over the years [18,32], local specialists informed us that treatments differ somewhat across hospitals. Therefore, together with these specialists, we revised the entire set of resource items to reflect the (average) current breast cancer treatment practices in Costa Rica. Specialists in Mexico had a similar opinion.

As its health care system has three main public institutions providing health care, treatment and reimbursement between these institutions may differ due to, for example, differences in salaries and drug prices. Hence we used resource utilization estimates of IMSS, which provides social insurance to approximately 40% of Mexico's population [33].

Whenever possible we used locally obtained costing data. When not available we applied the original WHO-CHOICE estimates for either country. These estimates are based on econometric analysis of a detailed WHO-CHOICE database from South Africa including a set of standard salaries, drugs, outpatient visits, materials and supplies, capacity utilization and transportation multipliers [34]. In Costa Rica, the CCSS provided readily available unit costs of most breast cancer procedures. For Mexico, contrary to Salomon et al. [35], who used the WHO-CHOICE original estimates on costs, in this study we used a detailed micro-costing exercise performed by IMSS [36].

Costs of the procedures used for Costa Rica and Mexico are listed in table 3. We also integrated evaluation costs of women presenting without breast cancer, included the costs of diagnosing all other stages (only for stages I-IV separately) and, regarding screening interventions, included costs for evaluating false positives.

For the program-level costs, which capture management, administrative, media and law-enforcement costs, and costs for training of healthcare personnel we used local salaries and WHO-CHOICE allocation rules for Costa Rica. For Mexico we used the standard WHO-CHOICE program cost estimates and allocation rules. Media and operating costs (i.e. prices for broadcasting, flyers, and posters) were provided by the CCSS in Costa Rica and the MoH in Mexico.

Training costs were primarily based on training the required health care workers for each intervention. We maintained the allocation assumptions listed in the WHO-CHOICE model as set by Zelle et al. [22] and used local salaries and WHO standard salaries for Costa Rica and Mexico respectively. In both countries all costs were estimated in 2009 local currency units (i.e. Costa Rican colones (CRC) and Mexican pesos (MXN)) and converted to U.S. dollars (US$) using the 2009 exchange rate (1.00US$ = 560.45CRC and 1.00US$ = 13.06MXN$) [34,35]. Both health effects (DALYs) and costs (US$) were discounted at a rate of 3% annually, which is recommended by WHO-CHOICE [8]. Working from a health care perspective we did not take into account travel and opportunity costs.

Table 3. *Average utilization of diagnosis and treatment ingredients and unit costs per patient*

Procedure	Ingredients	Stage I		Stage II		Stage III		Stage IV		Relapse		Palliative Care[g] (Extended)		Unit cost per patient (US$)	
		Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico
Initial diagnosis and evaluation during treatment	No. of health center visits	1	1	1	1	1	1	1	1	1	1			23,69 [a]	25,40 [c]
	No. of hospital visits	3	2	3	2	3	2	3	2	3	2			63,187 [a]	80,47 [c]
	Bilateral Mammography	1	1	1	1	2	1	-	-	-	-			45,44 [a]	42,27 [d]
	Complete blood count	7	7	7	7	7	7	7	7	6	6			17,50 [b]	10,34 [d]
	FNA or core needle biopsy	1	1	1	1	1	1	1	1	-	-			71,62 [a]	91,52 [c]
	Liver function tests	8	8	8	8	8	8	8	8	7	7			40,31 [a]	10,34 [d]
	Ultrasonography	1	1	1	1	1	1	1	1	-	-			23,65 [b]	48,32 [d]
	Renal function tests	8	8	8	8	8	8	8	8	7	7			9,81 [a]	10,34 [d]
	Bone scan	-	-	-	-	1	1	1	1	-	-			108,01 [b]	192,57 [d]
	Chest X-ray	1	1	1	1	1	1	1	1	-	-			16,11 [a]	14,93 [c]
	ECG	1	1	1	1	1	1	1	1	-	-			10,14 [b]	27,26 [f]
	Her2/neu test	1	1	1	1	1	1	1	1	-	-			27,73 [e]	32,70 [d]
Non-breast cancer evaluation	No. of health center visits	2	2	2	2	2	2	2	2					23,69 [a]	25,40 [c]
	Bilateral Mammography	1	1	1	1	1	1	1	1					45,44 [a]	42,27 [d]
	Ultrasonography	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28					22,68 [b]	22,59 [c]
	FNA or core needle biopsy	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02					71,62 [b]	91,52 [c]

Procedure	Ingredients	Stage I		Stage II		Stage III		Stage IV		Relapse		Palliative Care [g] (Extended)		Unit cost per patient (US$)	
		Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico
Treatment	No. of hospitalization days	2	2	2	2	2	2	6	0	6	0	6		134,55 [a]	292,11 [c]
	No. of OPD visits radiotherapy	30	0	30	0	30	0	30	0	30	0	1	0	63,16 [a]	80,47 [c]
	No. of OPD visits chemotherapy	6	7	6	7	6	7	6	7	6	7	-		63,16 [a]	80,47 [c]
	% receiving surgical intervention	Lumpectomy		Lumpectomy		Lumpectomy		Lumpectomy		Lumpectomy		Lumpectomy		239,33 [b]	805,59 [c]
		60%	80%	60%	0,40%	20%	0%	-	-	-	-	-	-		
		Mastectomy		Mastectomy		Mastectomy		Mastectomy		Mastectomy		Mastectomy		243,27 [b]	857,34 [d]
		40%	20%	40%	60%	80%	30%	10%	-	10%	-	5%	-		
	% receiving anesthesia	60%		70%		90%		5%	-	5%	-	5%	-	61,22 [b]	76,68 [c]
	% receiving radiotherapy [h]	70%	86%	70%	80%	100%	100%	30%	0%	30%	0%	-	-	500,52 [b]	438,20 [c]
	% receiving endocrine treatment [i]	61%	50%	61%	40%	61%	65%	61%	40%	61%	40%	61%	50%	0,04/day [a]	0,51 [d]
	% receiving chemotherapy [j]	0%	80%	20%	100%	60%	100%	60%	90%	80%	0%	-		1469,97 [a]	2327,20[c]
	% receiving boost radiotherapy [k]											41%	65%	71,23 [b]	106,16 [c]
	% receiving home based visits											75%	75%	23,69 [a]	25,40 [c]
	% receiving morphine [l]											84%	100%	0,59/day [a]	1,12 [c]
	% receiving laxative [m]											50%	47%	0,10/day [a]	0,03 [c]

Procedure	Ingredients	Stage I		Stage II		Stage III		Stage IV		Relapse		Palliative Care [g] (Extended)		Unit cost per patient (US$)	
		Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico	Costa Rica	Mexico
	% receiving Ondansetron [n]											36%	60%	2,80/day [a]	1,72 [c]
	% receiving Amitriptyline [o]											41%	100%	0,04 [a]	0,37 [c]
	% receiving Zelodronic Acid [p]							30%	30%	30%	30%	30%		200,00 [a]	260,18 [d]
	% receiving Trastuzumab	30%	11%	30%	14%	30%	21%	30%	19%	30%	7%			1800 [a]	1610 [c]

[a] *Based on estimates by Costa Rican CCSS;* [b] *Unit costs WHO-CHOICE database in 2000 US$. Corrected for inflation: 2000-2009 (2.81 in CR & 1.66 in MX). 2009 exchange rates were used (560.45 CRC/US$ & 13.06 MXN/US$);* [c] *Based on values of IMSS;* [d] *Based on communication with Unidad de Análisis Económico of MoH;* [e] *Based on Norum et al. [61];* [f] *Based on Knaul et al. [11];*

[g] *palliative care (substitutes stage IV treatment);* [h] *50 Gy given in 25 fractions of 2 Gy.;* [i] *daily dose of 20 mg.Tamoxifen for 5 years;* [j] *7 cycles of Epirubicin, Fluorouracil and cyclophosphamide (FEC regimen);* [k] *1 fraction of 10 Gy.;* [l] *40ml/54sdays;* [m] *35mg/54 days;* [n] *8mg/day;* [o] *75mg/day;* [p] *5 mg/day.*

Cost-effectiveness analysis

The average cost-effectiveness ratio (ACER) of each intervention is calculated by dividing the average costs of the intervention by average number of DALYs averted. These ACERs provide information on the set of interventions a region should finance to maximize health gains. The incremental cost-effectiveness ratios (ICERs) are calculated in relation to the last intervention purchased in each country, by dividing the incremental costs by the incremental health effects. These ICERs are used to establish an expansion path which shows the order in which the various interventions should be introduced if cost-effectiveness is the only consideration [39]. Only interventions with the lowest cost for additional effects are considered on this expansion path. WHO-CHOICE defines interventions that have a cost-effectiveness ratio of less than one times the gross domestic product (GDP) per capita as very cost-effective, and those with a ratio that falls between one and three times the GDP per capita as cost-effective [40]. In Costa Rica, this means that interventions that cost less than US$6,629 per DALY averted can be considered very cost-effective, and interventions that cost between US$6,629 and US$19,888 per DALY averted can be considered cost-effective. For Mexico these thresholds are US$8,416 and US$25,249 per DALY averted, respectively.

Sensitivity analysis

In line with Zelle et al. we performed a deterministic sensitivity analysis for both Costa Rica and Mexico to assess the impact of key parameters on our cost-effectiveness estimates [22]. In both countries we increased the DW's with 10%. Whereas costs of outpatient visits were increased by 25%, we raised the costs of mammography with 200%. In estimating the impact of various screening interventions we decreased the sensitivity of CBE and mammography by 25% and assumed attendance rates of screening of 60%. When available we also used alternative stage distributions for the current situation and different CFs. The unit costs for surgical procedures Costa Rica were much lower than those of Mexico. To test the impact of this we substituted these costs with the Mexican values.

Results

Table 4 shows the results for Costa Rica (panel A) and Mexico (panel B). Both costs, effects and cost-effectiveness are presented. In Figure 2 these results are presented graphically and the expansion paths are shown as black lines.

Costa Rica

Table 4 panel A shows the annual number of DALYs averted in treating the individual stages I-IV to vary between 193 (stage III) and 573 (stage II). Jointly these interventions in each stage can avert almost 1,400 DALYs per year. Adding palliative care only averts a small number of DALYs. The costs of treating the individual stages range between approximately US$4 million and US$5 million per year. Adding basic and extensive palliative care programs to stage IV treatment adds approximately US$0.1 and US$1 million to the yearly costs of stage IV treatment. At the 80% coverage level the current country situation in Costa Rica is highly cost-effective with an ICER below the country's GDP per capita, i.e. US$4,739/DALY. In expanding Costa Rica's breast cancer services, our analysis shows that treatment of all stages plus a CBE screening program targeting women between 40 and 70 years of age (I-IV + CBE (40-70)) is the next best option. At a total yearly cost of almost US$13 million, CBE averts 2,381 DALYs per year. This can be considered a very cost-effective intervention as the ICER of this intervention is below one time Costa Rica's GDP per DALY.

From figure 2 it follows that although the ACER of implementing mammography screening for women between 50-70 years is still below Costa Rica's GDP per capita per DALY, the ICER (as compared to CBE screening) is not lower than this threshold (i.e. the slope of the expansion path is steeper than US$6,629/DALY). While still considered a cost-effective intervention, mammography screening in age group 50-69 averts 2,619 DALYs per year at a yearly cost of US$16 million. Increasing the age group for mammography screening to women between 40-70 years shows a similar trend, i.e. averting 3,015 DALYs at an annual cost of US$21 million can be considered cost-effective. Adding Trastuzumab to this intervention, while resulting in the highest number of DALYs averted per year, i.e. 3,274 DALYs at a total yearly cost of US$29 million, is not considered cost-effective as its ICER is above the three times GDP per DALY threshold.

The combinations of various interventions are all close to the expansion path meaning they avert DALYs at a slightly less favorable ICER but could nevertheless be meaningful to implement. For example, expanding the current program's coverage to reach 95% or implementing a Mass-media Awareness Raising program (MAR), could be interesting options if the available budget is not sufficient to implement a screening strategy.

Mexico

Table 4 panel B shows that the annual number of DALYs averted in the individual stages I-IV varies between 1,503 (stage IV) and 10,629 (stage II). Jointly these interventions in each stage avert approximately 26,000 DALYs per year. The addition of palliative care does not gain much health.

With an ACER of US$5,715 the current situation with 70% coverage is very cost-effective. The analysis shows it is better to increase the coverage level of the current intervention to 95% instead of adding Trastuzumab. In our analysis, implementing a program of Mass-media awareness raising (MAR) buys health most efficiently. Our results show that MAR averts 32,908 DALYs per year at a yearly cost of US$165 million, which leads to an ACER of US$5,021 per DALY averted. When a higher budget would be available, implementing mammography screening for women aged 50-70 would be the first next step. This intervention averts 44,192 DALYs per year at an estimated yearly cost of US$310 million. Even more resources would allow to subsequently add Trastuzumab and increase the age group to 40-70. These interventions fill out the expansion path and avert 47,616 and 50,714 DALYs per year at an estimated yearly cost of US$358 and US$471 million respectively. It should be noted that a CBE screening program, with an expected health gain of 39,769 DALYs averted at a cost of US$260 million, could be an interesting 'in-between' option.

Table 4. *Average costs (US$), effects and cost-effectiveness of breast cancer control scenarios per year*

Panel A: Costa Rica

No.	Description of intervention	Patients per year	Annual patient costs[a]	Annual program costs	Annual training costs	Annual total costs	DALYs averted per year[b]	ACER[c]	ICER[d]
1	Current country specific situation (80%)	940	4,569,310	646,358	6,660	5,222,329	1,102	4,739	4,739
2	Stage I to IV treatment (current) + Trastuzumab (80%)	940	11,708,670	646,358	6,660	12,361,689	1,347	9,180	NA
3	Stage I treatment + relapse (95%)	163	2,862,111	854,431	7,439	3,723,980	404	9,218	NA
4	Stage II treatment + relapse (95%)	464	4,303,195	854,431	7,439	5,165,065	573	9,007	NA
5	Stage III treatment + relapse (95%)	235	3,884,520	854,431	7,439	4,746,390	193	24,587	NA
6	Stage IV treatment (95%)	261	3,107,345	854,431	7,439	3,969,215	162	24,559	NA
7	Basic Palliative Care (BPC) (95%)	261	2,466,328	1,583,922	27,897	4,078,147	163	25,078	NA
8	Extended Palliative Care (EPC) (95%)	261	3,160,703	2,022,956	27,897	5,211,556	164	31,852	NA
9	Stage I to IV treatment combined (current 95%)	1,116	5,659,297	1,421,412	7,439	7,088,148	1,309	5,417	NA
10	Biennial mammography screening (50-70) + treatment of stage I to IV (95%)	1,116	12,498,059	3,792,653	22,317	16,313,029	2,619	6,228	NA
11	Biennial mammography screening (50-70) + treatment of stage I to IV + Trastuzumab (95%)	1,116	20,438,042	3,792,653	22,317	24,253,012	2,886	8,402	NA
12	Biennial mammography screening (40-70) + treatment of stage I to IV (95%)	1,116	17,546,792	3,792,522	22,317	21,361,632	3,015	7,085	13,426
13	Biennial mammography screening (40-70) + treatment of stage I to IV + Trastuzumab (95%)	1,116	25,401,093	3,792,522	22,317	29,215,932	3,274	8,924	30,352
14	Basic awareness outreach program + Mass-media Awareness Raising (MAR) + treatment of stage I to IV (95%)	1,116	6,158,209	4,519,154	11,159	10,688,521	1,825	5,857	NA
15	Biennial Clinical Breast Examination (CBE) screening (40-70) + treatment of stage I to IV (95%)	1,116	9,255,065	3,576,629	20,086	12,851,779	2,381	5,397	5,964
16	MAR + BPC + treatment of stage I to III (95%)	1,116	6,262,398	4,733,109	39,055	11,034,563	1,826	6,044	NA

Panel A: Costa Rica

No.	Description of intervention	Patients per year	Annual patient costs[a]	Annual program costs	Annual training costs	Annual total costs	DALYs averted per year[b]	ACER[c]	ICER[d]
17	Biennial CBE Screening + BPC + treatment of stage I to III (95%)	1,116	9,422,391	3,426,610	47,982	12,896,984	2,382	5,415	NA
18	Biennial mammography Screening (40-70) + BPC + treatment stage I to III (95%)	1,116	17,578,700	4,170,935	50,214	21,799,850	3,016	7,229	NA
19	Biennial mammography Screening (50-70) + EPC + treatment of stage I to III (95%)	1,116	12,620,626	4,215,537	50,214	16,886,376	2,621	6,444	NA

*[a] All costs in this table are in 2009 US$ (1CRC = 0,001784 US$); [b] DALYs, disability-adjusted life-years (age weighted, discounted); [c] **ACER** = average cost-effectiveness ratio compared to the do nothing-scenario (US$ per DALY averted); [d] **ICER** = Incremental cost effectiveness ratio, ratio of additional cost per additional life-year saved when next intervention is added to a mix on the intervention path (additional US$ per additional DALY saved).*

Panel B: Mexico

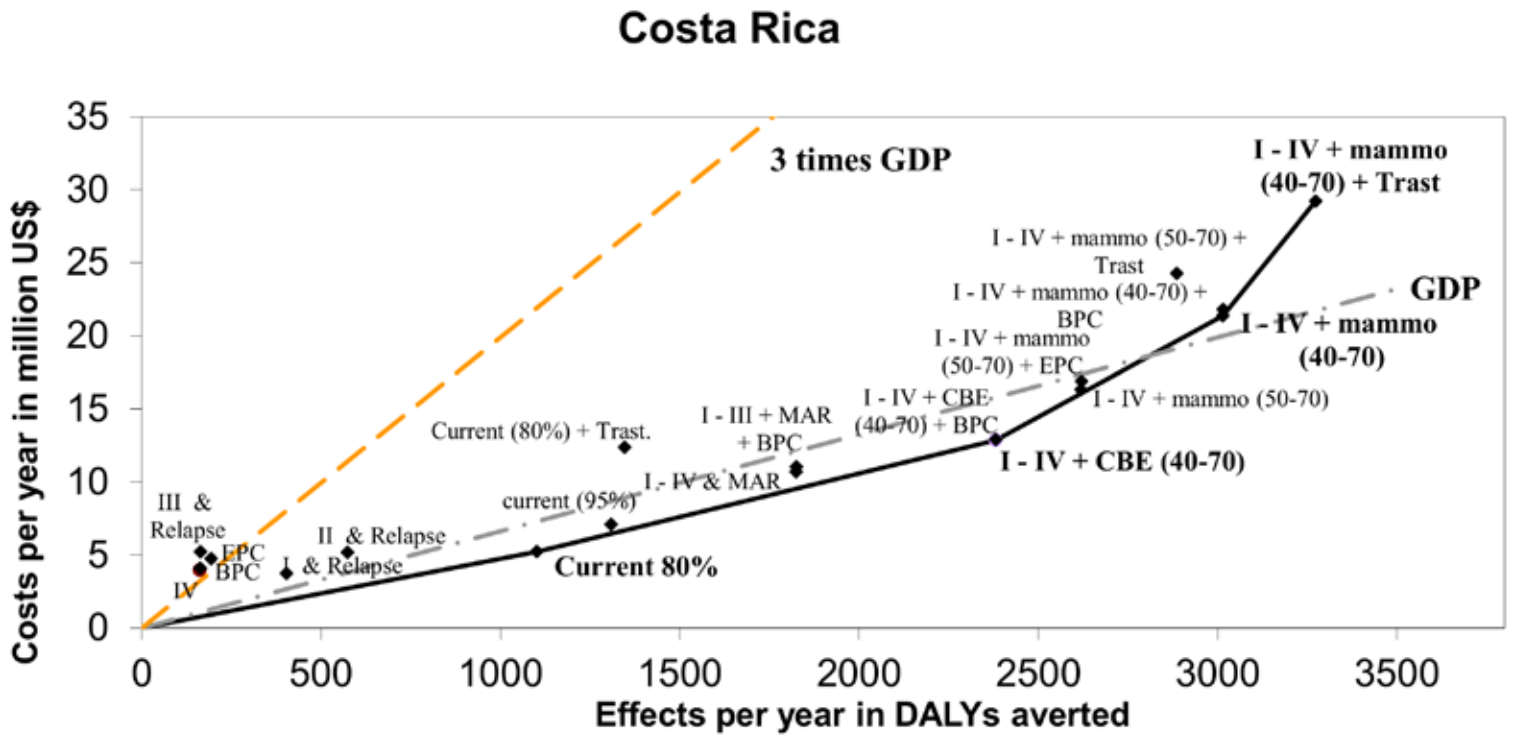
No.	Description of intervention	Patients per year	Annual patient costs[a]	Annual program costs	Annual training costs	Annual total costs	DALYs averted per year[b]	ACER[c]	ICER[d]
1	Current country specific situation (80%)	940	4,569,310	646,358	6,660	5,222,329	1,102	4,739	4,739
2	Stage I to IV treatment (current) + Trastuzumab (80%)	940	11,708,670	646,358	6,660	12,361,689	1,347	9,180	NA
3	Stage I treatment + relapse (95%)	163	2,862,111	854,431	7,439	3,723,980	404	9,218	NA
4	Stage II treatment + relapse (95%)	464	4,303,195	854,431	7,439	5,165,065	573	9,007	NA
5	Stage III treatment + relapse (95%)	235	3,884,520	854,431	7,439	4,746,390	193	24,587	NA
6	Stage IV treatment (95%)	261	3,107,345	854,431	7,439	3,969,215	162	24,559	NA
7	Basic Palliative Care (BPC) (95%)	261	2,466,328	1,583,922	27,897	4,078,147	163	25,078	NA
8	Extended Palliative Care (EPC) (95%)	261	3,160,703	2,022,956	27,897	5,211,556	164	31,852	NA
9	Stage I to IV treatment combined (current 95%)	1,116	5,659,297	1,421,412	7,439	7,088,148	1,309	5,417	NA
10	Biennial mammography screening (50-70) + treatment of stage I to IV (95%)	1,116	12,498,059	3,792,653	22,317	16,313,029	2,619	6,228	NA

Panel B: Mexico

No.	Description of intervention	Patients per year	Annual patient costs[a]	Annual program costs	Annual training costs	Annual total costs	DALYs averted per year[b]	ACER[c]	ICER[d]
11	Biennial mammography screening (50-70) + treatment of stage I to IV + Trastuzumab (95%)	1,116	20,438,042	3,792,653	22,317	24,253,012	2,886	8,402	NA
12	Biennial mammography screening (40-70) + treatment of stage I to IV (95%)	1,116	17,546,792	3,792,522	22,317	21,361,632	3,015	7,085	13,426
13	Biennial mammography screening (40-70) + treatment of stage I to IV + Trastuzumab (95%)	1,116	25,401,093	3,792,522	22,317	29,215,932	3,274	8,924	30,352
14	Basic awareness outreach program + Mass-media Awareness Raising (MAR) + treatment of stage I to IV (95%)	1,116	6,158,209	4,519,154	11,159	10,688,521	1,825	5,857	NA
15	Biennial Clinical Breast Examination (CBE) screening (40-70) + treatment of stage I to IV (95%)	1,116	9,255,065	3,576,629	20,086	12,851,779	2,381	5,397	5,964
16	MAR + BPC + treatment of stage I to III (95%)	1,116	6,262,398	4,733,109	39,055	11,034,563	1,826	6,044	NA
17	Biennial CBE Screening + BPC + treatment of stage I to III (95%)	1,116	9,422,391	3,426,610	47,982	12,896,984	2,382	5,415	NA
18	Biennial mammography Screening (40-70) + BPC + treatment stage I to III (95%)	1,116	17,578,700	4,170,935	50,214	21,799,850	3,016	7,229	NA
19	Biennial mammography Screening (50-70) + EPC + treatment of stage I to III (95%)	1,116	12,620,626	4,215,537	50,214	16,886,376	2,621	6,444	NA

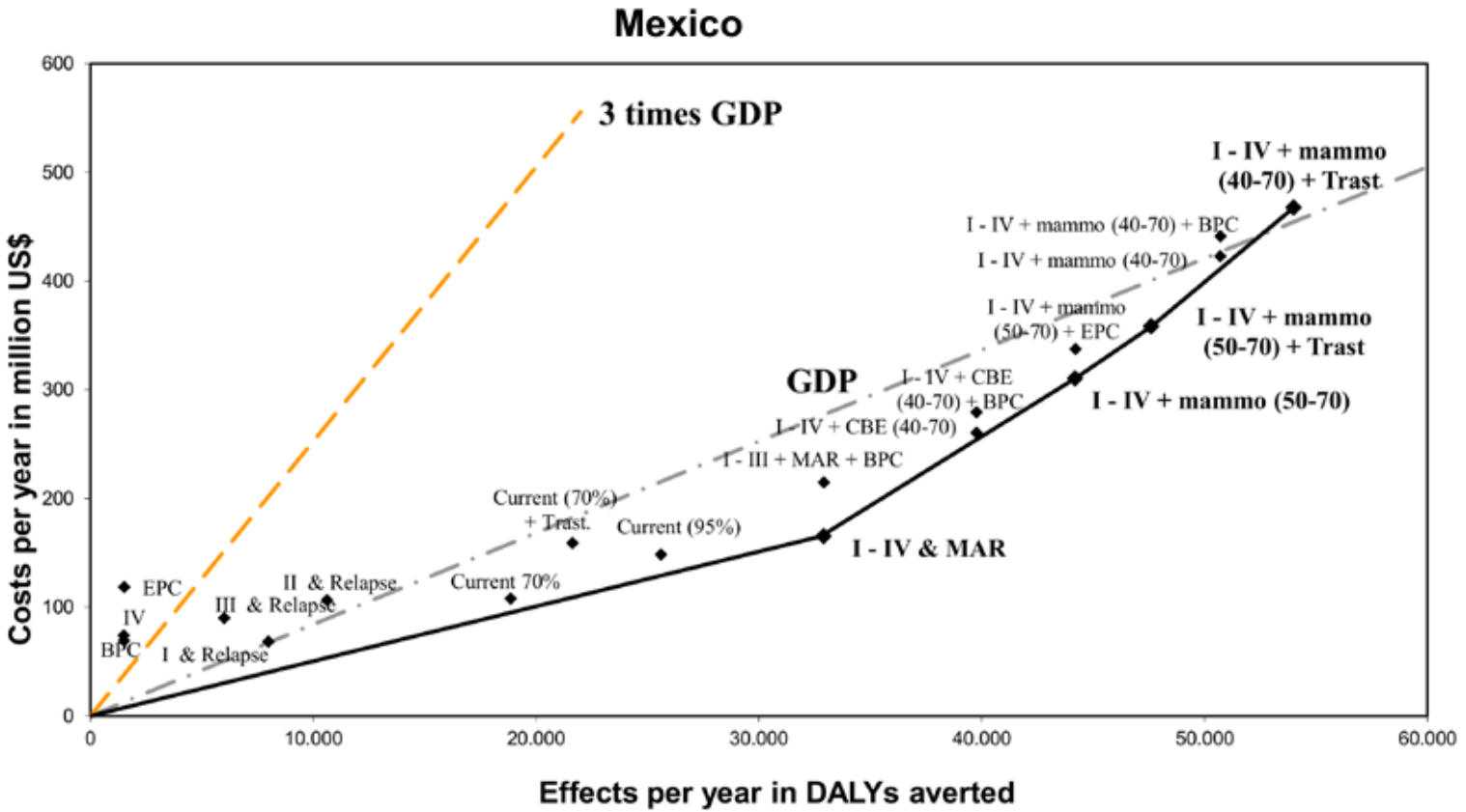
*[a] All costs in this table are in 2009 US$ (1MXN = 0,0765697 US$); [b] DALYs, disability-adjusted life-years (age weighted, discounted); [c] **ACER**= Average cost-effectiveness ratio compared to the do nothing-scenario (US$ per DALY averted). [d] **ICER** = Incremental cost effectiveness ratio, ratio of additional cost per additional life-year saved when next intervention is added to a mix on the intervention path (additional US$ per additional DALY saved).*

Figure 2. *Cost-effectiveness of breast cancer interventions and expansion path according to Incremental Cost-Effectiveness Ratios for Costa Rica*



Dotted lines represent cost-effectiveness threshold of 1 and 3 times 2009 GDP/capita, i.e. 6,629 US$/DALY and 19,888 US$/DALY [37,38].

Figure 3. *Cost-effectiveness of breast cancer interventions and expansion path according to Incremental Cost-Effectiveness Ratios for Mexico.*



Dotted lines represent cost-effectiveness threshold of 1 and 3 times 2009 GDP/capita, i.e. 8,416 US$/DALY and 25,249 US$/DALY [37,38].

Sensitivity analysis

Sensitivity analysis showed our results to be particularly sensitive to different assumptions on stage distribution at presentation and case fatality rates (Table 5). The Costa Rican CFs we obtained from Ortiz [24] differed strongly from those we deem to reflect technical efficiency [7,22]. Using these CFs causes the ACERs to vary between minus 82.7% for stage I and plus 65.5% for stage II. With regards to the current stage distribution, for Costa Rica we used the distribution from Groot et al. [7]. With this less favorable stage distribution, the current country situation was not part of the expansion path anymore. Rather, the CBE screening program now became the most cost-effective.

For Mexico we ran the model with three different current stage distributions obtained from different studies [7,41,42]. These different stage distributions caused the ACERs to increase between 0 – 15%. When using the higher CFs from Salomon et al. [35] for the intervention scenarios, the ACERs increased to a larger extent (34.7% for the current country situation).

For both countries, changes in the other parameters also led to different outcomes although their impact was smaller. For example, in Costa Rica the WHO default unit costs for a mastectomy or a lumpectomy were relatively low. Unable to obtain these unit costs from Costa Rica, using the higher Mexican unit costs showed their impact on the ACERs to be marginal.

Table 5. *Results of sensitivity analysis on average cost-effectiveness ratio (ACER)*

Panel A: Costa Rica												
	Intervention scenarios	ACER	Alternative stage distribution[a]	Case fatality rates[b]	Disability weights +10%	Costs outpatient visits +25%	Costs mammography +200%	Costs mastectomy Mexico	Costs lumpectomy Mexico	Capacity utilization equipment 25%c	Sensitivity of CBE and mammography -25%d	Attendance rates screening program 60%
1	Current country specific situation 80%	4,739	5,519	4,447	5,132	4,882	6,218	4,931	4,901	4,739		
2	Stage I to IV treatment combined (current 80%) + Trastuzumab	9,180	9,838	8,226	9,796	9,325	10,402	9,337	9,313	9,180		
3	Stage I treatment	9,218	11,569	53,348	13,846	9,690	13,096	9,308	9,340	9,218		
4	Stage II treatment	9,007	16,395	5,442	9,605	9,369	12,032	9,183	9,250	9,007		
5	Stage III treatment	24,587	7,630	19,686	26,352	25,608	33,092	25,133	24,709	24,587		
6	Stage IV treatment	24,559	29,195	25,869	26,307	25,774	33,715	24,646	24,559	24,559		
7	Basic Palliative Care (BPC)	25,078	30,875	26,412	26,833	26,248	34,179	25,121	25,078	25,078		
8	Extended Palliative Care (EPC)	31,852	38,068	33,542	34,044	33,245	40,897	31,895	31,852	31,852		
9	Stage I to IV treatment combined (current 95%)	5,417	6,254	5,082	5,866	5,592	6,895	5,609	5,579	5,417		
10	Biennial mammography screening (50-70 years) + Stage I to IV treatment	6,228	4,464	7,060	6,565	6,538	10,589	6,336	6,330	6,228	7,535	7,723
11	Biennial mammography screening (50-70 years) + Stage I to IV treatment + Trastuzumab	8,402	6,251	9,013	8,807	8,684	12,365	8,501	8,495	8,402	9,856	10,058
12	Biennial mammography screening (40-70 years) + Stage I to IV treatment	7,085	5,216	8,069	7,433	7,496	13,203	7,174	7,182	7,085	7,677	8,114
13	Biennial mammography screening (40-70 years) + Stage I to IV treatment + Trastuzumab	8,924	6,769	9,674	9,322	9,303	14,562	9,006	9,014	8,924	9,566	10,031
14	Mass media awareness raising (MAR) + treatment of stage I to IV	5,857	3,965	5,947	6,247	6,017	7,232	6,010	5,987	5,857		

Panel A: Costa Rica												
	Intervention scenarios	ACER	Alternative stage distribution[a]	Case fatality rates[b]	Disability weights +10%	Costs outpatient visits +25%	Costs mammography +200%	Costs mastectomy Mexico	Costs lumpectomy Mexico	Capacity utilization equipment 25%c	Sensitivity of CBE and mammography -25%d	Attendance rates screening program 60%
15	Biennial clinical breast examination (CBE) screening (40–69) + treatment of stage I to IV	5,397	3,794	6,095	5,710	5,916	5,977	5,520	5,503	5,397	6,881	7,028
16	MAR + BPC + Stage I to III treatment	6,044	4,092	6,137	6,446	6,206	7,418	6,195	6,174	6,044		
17	Biennial CBE screening (40–69) + BPC + treatment of stage I to III	5,415	3,806	6,115	5,728	5,934	5,994	5,537	5,520	5,415	6,919	7,068
18	Biennial mammography screening (40–69) + BPC + treatment of stage I to III	7,229	5,323	8,232	7,583	7,641	13,345	7,318	7,326	7,229	7,836	8,284
19	Biennial mammography screening (50–69) + EPC + treatment of stage I to III	6,444	4,619	7,304	6,792	6,756	10,803	6,551	6,545	6,444	7,815	8,013

Panel A. (Costa Rica). Alternative stage distribution = 9.4% stage I, 14.2% stage II, 58.0% stage III, 18.4% stage IV[7]; b Alternative Case Fatality rates = 0,0174 stage I, 0,0284 stage II, 0,0832 stage III, 0,2855 stage IV 24; c Mechanical equipment (e.g. mammography machines, CT, X-ray); d Alternative assumptions on effectiveness of awareness interventions (-25%), sensitivity of CBE, and stage shifts of CBE screening.

Panel A: Costa Rica												
	Intervention scenarios	ACER	Alternative stage distribution[a]	Case fatality rates[b]	Disability weights +10%	Costs outpatient visits +25%	Costs mammography +200%	Costs mastectomy Mexico	Costs lumpectomy Mexico	Capacity utilization equipment 25%c	Sensitivity of CBE and mammography -25%d	Attendance rates screening program 60%
1	Current country specific situation 70%	5,715	6,081	6,576	5,742	7,696	7,764	5,865	6,861	5,713		
2	Stage I to IV treatment combined (current 70%) + Trastuzumab	7,344	7,405	7,330	7,513	9,031	8,768	7,482	8,400	7,342		
3	Stage I treatment	8,541	11,835	11,407	9,745	19,263	11,997	8,933	11,407	8,534		
4	Stage II treatment	10,021	9,613	9,026	16,334	11,433	14,721	10,326	12,416	10,014		
5	Stage III treatment	14,960	12,661	15,139	9,786	18,509	31,038	15,515	19,071	14,950		
6	Stage IV treatment	49,231	55,817	169,157	37,773	46,698	52,548	51,336	63,668	49,192		
7	Basic Palliative Care (BPC)	45,609	53,896	195,026	31,995	43,268	48,621	47,661	59,946	45,569		
8	Extended Palliative Care (EPC)	77,813	85,844	229,906	62,358	73,858	82,886	80,085	92,056	77,774		
9	Stage I to IV treatment combined (current 95%)	5,796	6,168	6,673	5,820	7,804	7,874	5,946	6,942	5,793		
10	Biennial mammography screening (50-70 years) + Stage I to IV treatment	7,025	5,703	8,161	4,043	9,059	7,649	7,397	11,541	7,023	10,041	10,567
11	Biennial mammography screening (50-70 years) + Stage I to IV treatment + Trastuzumab	7,526	6,261	8,495	4,607	9,462	8,108	7,526	7,526	7,526	10,051	10,460
12	Biennial mammography screening (40-70 years) + Stage I to IV treatment	8,339	6,992	9,425	5,169	10,572	8,945	8,863	15,109	8,338	9,525	10,509
13	Biennial mammography screening (40-70 years) + Stage I to IV treatment + Trastuzumab	8,659	7,377	9,599	5,602	10,859	9,226	9,148	14,974	8,658	9,821	10,688
14	Mass media awareness raising (MAR) + treatment of stage I to IV	5,021	3,656	6,503	2,293	6,604	5,799	5,172	6,186	5,019		

Panel A: Costa Rica												
	Intervention scenarios	ACER	Alternative stage distribution[a]	Case fatality rates[b]	Disability weights +10%	Costs outpatient visits +25%	Costs mammography +200%	Costs mastectomy Mexico	Costs lumpectomy Mexico	Capacity utilization equipment 25%c	Sensitivity of CBE and mammography -25%d	Attendance rates screening program 60%
15	Biennial clinical breast examination (CBE) screening (40–69) + treatment of stage I to IV	6,550	5,149	7,837	3,510	8,579	7,246	7,218	7,097	6,549	11,097	11,711
16	MAR + BPC + Stage I to III treatment	6,522	4,751	8,452	2,981	8,661	7,531	6,671	7,613	6,520		
17	Biennial CBE screening (40–69) + BPC + treatment of stage I to III	7,021	5,519	8,402	3,763	9,195	7,766	7,690	7,568	7,019	12,194	12,893
18	Biennial mammography screening (40–69) + BPC + treatment of stage I to III	8,701	7,296	9,836	5,394	11,023	9,333	9,226	15,490	8,700	10,010	11,103
19	Biennial mammography screening (50–69) + EPC + treatment of stage I to III	7,634	6,200	8,874	4,395	9,844	8,312	8,009	12,149	7,633	11,152	11,765

Panel B (Mexico). Unidad de Análisis Económico - 8.4% stage I, 38.5% stage II, 42.5% stage III, 10.6% stage IV [42]; b 9.7% stage I, 52.7% stage II, 34.8% stage III, 2.8% stage IV 41; c 9.4% stage I, 14.2% stage II, 58.0% stage III, 18.4% stage IV 7; d Alternative Case Fatality rates: 0,013 stage I, 0,042 stage II, 0,102 stage III, 0,266 stage IV 35; e Mechanical equipment (e.g. mammography machines, CT, X-ray); f Alternative assumptions on effectiveness of awareness interventions (-25%), sensitivity of CBE, and stage shifts of CBE screening.

Discussion

Our results indicate that in both Costa Rica and Mexico treating stage IV disease only, or treating stage IV and providing basic or extended palliative care is not cost-effective. In general, interventions ensuring more patients to present at the hospital in earlier stages seem the most cost-effective.
These results are in line with other studies which find mammography screening for women aged 50-70 to be cost-effective in sub-Saharan Africa and South East Asia [7,43]. Although Ginsberg et al. did not study the cost-effectiveness of clinical breast examination or other awareness raising programs, they acknowledge less expensive means of early detection in limited resource settings could be cost-effective in LMICs [43]. When modeling the expected outcomes of such strategies - though based on limited evidence - Zelle et al. find that CBE screening or mass media awareness raising interventions seem indeed cost-effective in Ghana [22].

Although mammography interventions can be considered cost-effective, their total annual costs (budget impact) are high and may therefore not be appropriate for wide scale implementation.
If the necessary resources are not available both countries could choose to lower coverage levels or implement interventions with comparable ACERs (buying health just as efficiently) but with lower budget impact. For Costa Rica, our analysis shows the most cost-effective option for expanding the current breast cancer services would be a CBE screening program combined with treatment of all stages. The yearly costs of this program are about US$12 million. In 2009, the per capita health expenditure in Costa Rica was US$660 (10.3% of total GDP) [37]. With a population of approximately 4.5 million, implementing a CBE screening program would add US$2.82 to this amount (0.43% increase). Although this increase may seem feasible, the implementation and effectiveness of this program is highly dependent on the availability of human resources and the capacity of the healthcare system to refer and treat all new-found cases [44-46]. Also, if the implementation of a CBE screening program would be unfeasible, MAR could be an interesting option as it is slightly less cost-effective but has a smaller yearly budget impact (US$10 million). Yet, the very limited evidence on MAR's effectiveness requires our estimates to be interpreted with caution. Implementing a screening program for which the evidence base is stronger (e.g. mammography for women between 50-70 years of age) could be recommended if the yearly costs of US$16 million are affordable. Mammography screening in age group 40-70 costs much more (about US$21 million) and is therefore less economically attractive.

The Mexican MoH already decided to start increasing the use of the available infrastructure and mammography equipment for the population most at risk (women 50 to 70 years old and women with more than two risk factors). The gradual expansion will give enough time to train the required human resources. From our analysis the yearly costs of a mammography screening program for women 50-70 years of age at 95% coverage eventually would be US$310 million per year, a threefold increase over the current scenario. Next, once a reasonable increase on coverage would be reached the Mexican MoH plans to increase the coverage rate to women between 40-49 years of age [47]. According to our estimates the yearly costs of implementing such a program would be US$422 million. With approximately 110 million inhabitants and a per capita health expenditure of US$525 in 2009 (6.43% of total GDP) [37], implementing these programs would add US$2.82 (0.54% increase) and US$3.84 (0.72% increase) respectively to per capita health expenditure.

However, our analysis shows perhaps that strengthening actual MAR or CBE screening programs to be a more attractive first step in improving breast cancer services from an economic perspective. With yearly costs of US$165 and US$260 million if started from zero, the strengthening of existing programs is more affordable and more politically feasible as it would represent modest increases to existing budgets.
One of the principal questions we received from policy makers in both Costa Rica and Mexico concerned the addition of Trastuzumab to the treatment regimens. In Costa Rica we assumed 30% of the breast cancer patients have overexpression of the HER2/neu+ gene and are eligible for Trastuzumab [48]. As a result of adding Trastuzumab, in Costa Rica between 230 – 270 extra DALYs/year are averted at an additional cost of approximately US$7 million per year. For Mexico we obtained the actual proportion of patients receiving Trastuzumab in IMSS. Here the health gains comprise between 2,800 and 3,400 extra DALYs/year averted and the additional costs fall between US$45 – 51 million. It is worth noting that in Mexico Trastuzumab is already provided as part of the treatment for all eligible women in stages I to IV. Our analysis shows the addition of this bio-pharmaceutical to increase the cost of treatment of stages I to IV by more than 48%, generating the need of developing public policies focused on negotiating price reductions that can contribute to the mid- and long-term financial sustainability. The use of tools as the ones presented in this paper can provide technical evidence on the benchmark price that the Mexican health system could use in negotiations considering the threshold of one times the GDP per capita.

The limitations regarding the model are essentially the same as those reported in previous studies [7,22]. First, as evidence on the effectiveness of awareness raising, CBE and mammography screening in Costa Rica and Mexico were absent, we relied on the same model approach as used by Zelle et al. [22]. Second, when calculating unit costs for Mexico we did not account for the mark up of transportation costs (as generally recommended by WHO-CHOICE) and did not include the costs of facilities. Including these costs would have probably resulted in slightly higher unit costs. Third, in adopting a health care perspective we did not take into account travel and opportunity costs. Including these costs would probably have increased costs generally. Fourth, we did not carry out a probabilistic sensitivity analysis. Carrying out such analysis would have shown worse ACERs when parameters are jointly changed in the negative direction (i.e. higher CFs and costs / worse stage distribution). Nonetheless, our deterministic sensitivity analysis shows the direction in which ACERs would change is clear and our general conclusions remain the same although the ranges of several ACERs are overlapping. The limitations fit within the overall goal of WHO-CHOICE which is to provide general indications of cost-effectiveness, i.e. not precise estimates of specific interventions.

In summary, for improving their current breast cancer control programs, our analysis suggests that both Costa Rica and Mexico would benefit from implementing strategies that advance early detection. For these countries, a mass-media awareness raising program and/or a CBE screening program coupled with treatment of all stages and careful monitoring and evaluation could be feasible options. If these strategies are implemented, the provision of breast cancer diagnostic, referral, treatment and, when possible, basic palliative care services is essential and should be facilitated simultaneously.

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6

CHAPTER 7

Cost-effectiveness of Breast Cancer Treatment in Maharashtra, India

Nothing is comprehensible except by virtue of its edge

(Indian proverb)

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Submitted

Abstract

Background

Breast cancer in India in an increasing public health problem. Costs of breast cancer treatment, in particular costs of systemic therapy, play an increasingly important role and this is accompanied by high out-of-pocket expenditure. As India has low financial resources, it is important to select cost-effective interventions. Our aim is to assess the cost-effectiveness of breast cancer treatment, with the focus on the impact of systemic therapy prices on this, and to investigate which price reductions are required for breast cancer treatment to be considered cost-effective.

Methods

We performed cost-effectiveness analysis from a health care perspective according to WHO-CHOICE standardised methods with costs expressed in United States Dollars (US$) and effects in disability adjusted life years (DALYs) averted. We used the BRC PopMod v4 model to simulate costs and effects for 21 different treatment scenarios. Analyses were based on demographic, epidemiological, economic and breast cancer specific data specific for the region Maharashtra, to the extent they were available.

Results

Treatments including only chemotherapy and hormone therapy cost annually 416 million to 689 million US$ and can avert up to 262,776 DALYs per year. Scenarios including a combination of chemotherapy, hormone therapy and taxanes avert maximal 268,173 DALYs per year and annual cost vary from 675 to 943 million US$. Interventions including trastuzumab (and taxanes) are most expensive and can costs up to 2.5 billion a year, but avert less DALYs per year, e.g. 248,088.

Conclusions

Only AC combined with tamoxifen and secondly, CAF combined with tamoxifen, can be considered cost-effective (ICERs are 1,840 and 5,102 US$ per DALY averted respectively). Interventions including taxanes and/or trastuzumab are not recommended for implementation. Trastuzumab prices need to be a 50 fold lower to be considered cost-effective. Achieving these reductions could be considered by the Indian government, as it is able to influence the drug market through policy making.

Introduction

Breast cancer is an increasing public health problem in India and has emerged as the leading type of female cancer in most urban populations in India 1. Trend evaluations have shown a significant increase of breast cancer incidence from 1976 to 2005 and in 2008 incidence was 162 cases per 100,000 females (Table 1) [2]. Moreover, approximately 666.000 disability adjusted life years (DALYs) are lost every year due to breast cancer in India [3].

Causes for these increasing numbers and the high amount of burden of disease (BOD) in India are transitions in (socio-)economic factors, urbanization, modernization and change of diet. These transitions may lead to a lifestyle entailing more risk factors for breast cancer. High burden of disease is caused by poor breast cancer outcomes, due to advanced clinical stage at diagnosis [4-7]. Additionally, the costs of breast cancer treatment play an increasingly important role. Not only is the economic burden of breast cancer considerably high, in addition to this, 59% from the total expenditure on health care is out-of-pocket in India [8, 9]. The largest cost are represented by drugs for systemic treatment and these are, hence, less accessible to Indian breast cancer patients.

In response to these high drug prices and the high burden of disease, the Indian government eliminated patents on drugs by introducing the Indian Patent Act in 1970, enabling the country to produce generic drugs at low cost. When India joined the World Trade Organisation in 1995, it was forced to adjust national laws and practices to the terms of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS). Currently, pharmaceutical companies can be forced by the Indian government to grant compulsory licenses to generic drug manufacturers, which enables these companies to produce drugs at low costs [10-12].

Besides controlling the costs of drugs for systemic therapy, given the impact of breast cancer on health care utilization and the financial constraints in India, it is necessary to identify cost-effective interventions that reduce the burden of breast cancer. However, economic evidence on breast cancer treatment in low- and middle-income countries such as India is currently lacking, as it has poor availability, quality and comparability [13].

The aim of this study is to provide evidence based information on the cost-effectiveness of breast cancer treatment in Maharashtra, India. We focus on the impact of systemic drug prices on this cost-effectiveness. This information can be used to investigate which price reductions are required to make breast cancer treatment more cost-effective. The results could be important for the Indian government, since it is able to influence the drug market through policy making and law-enforcement.

Table 1. *Age distribution of breast cancer incidence and mortality India*

Age groups	Female population*	Incidence (/100.000)	Number of incident cases (%)	Mortality (/100.000)	Number of deaths (%)	Mortality/incidence ratio
0-14	178,622,740	0.0	5 (0.0%)	0.0	0 (0.0%)	n/a
15-29	149,709,824	1.0	1,505 (1.7%)	0.3	392 (0.7%)	0.26
30-44	106,264,174	19.2	20,380 (22.8%)	6.1	6,437 (11.4%)	0.32
45-59	68,440,591	42.4	29,037 (32.4%)	25.2	17,264 (30.7%)	0.59
60-69	25,953,999	69.2	17,971 (20.1%)	52.6	13,643 (24.3%)	0.76
70-79	13,681,782	94.7	12,954 (14.5%)	79.2	10,829 (19.3%)	0.84
80+	4,111,983	187.3	7,701 (8.6%)	186.5	7,669 (13.6%)	1.00

Source: WHO Global Burden of Disease data 2004 update [3]

** Based on UN population 2005* [14]

Methods

General approach

We performed cost-effectiveness analyses using WHO-CHOICE standardised methods. This approach compares the costs and effects of all possible existing and new intervention scenarios to a counterfactual null, which is defined as a reference situation in which no interventions are available [15].

Interventions/scenarios

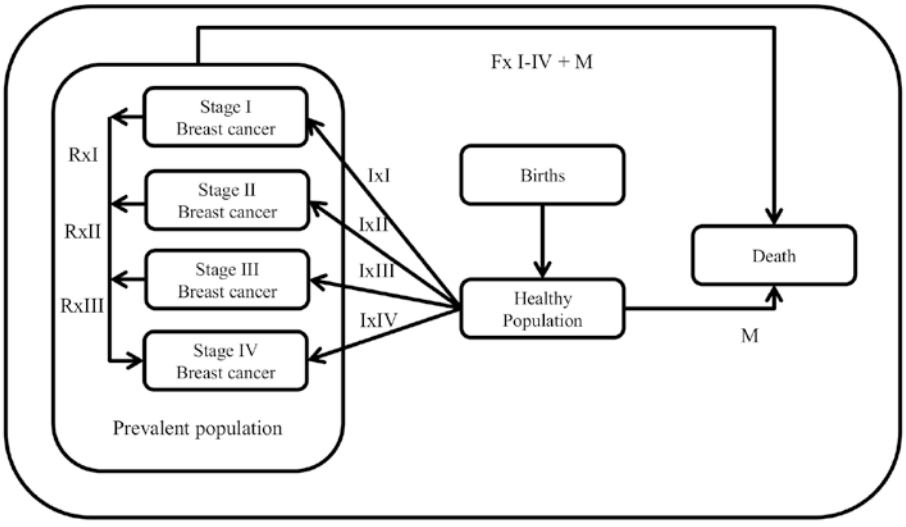
An expert panel, including representatives of the Tata Memorial Centre (TMC), the World Health Organization (WHO), and the Radboud University Nijmegen Medical Centre, defined 21 intervention scenarios for the systemic treatment of breast cancer in women. These intervention combinations include chemotherapy (CMF/AC/CAF and/or taxanes and/or trastuzumab), endocrine therapy (tamoxifen, aromatase inhibitors and switch therapy) and additional drugs, such as biphosphanates (Table 2). Following several breast cancer treatment guidelines [16-18] and data on average age [6], weight and height, we determined the dosage of each drug for the average Indian female breast cancer patient (Table 2). The scenarios are evaluated at 95% coverage level (i.e. reaching 95% of those who need the service) according to standard CHOICE methodology.

Mathematical model

The BRC PopMod v4 model was used to conduct the analysis. Demographic and epidemiological data, breast cancer specific data and data on costs and effects were entered into the model to calculate the cost-effectiveness ratios of the 21 scenarios.

The model structure is presented in Figure 1 [19, 20]. The model simulates the development of the Indian population in terms of births, background mortality and breast cancer epidemiology. The structure is built up from several components, which represent the sick population (AJCC breast cancers stages I-IV) [21], healthy population and a deceased state (death).

Figure 1. *Graphical representation of the model*



Graphical representation of the model. showing the relationships between the different health states through the incidence rates of breast cancer (ix1–ix4), the different stage-specific case-fatality rates (corrected for progression) (Fx1–4) and the background mortality (M). Stage-specific disability weights (Rx1–Rx3) are equal for all intervention scenarios and patients have relapse to stage IV at a constant rate [19,20].

The effectiveness of the intervention scenarios is based on case fatality and disability weights. All interventions are implemented for a period of 10 years, after which epidemiological rates return to their counterfactual level of no intervention. The model's population, however, is followed for another 90 years (100 years total), as the health effects of interventions are visible years after the period of implementation. Population health gains in DALYs averted are calculated as the difference in total number of healthy life years lived by the population between each treatment scenario and the null scenario after a 100 years [19]. DALYs were age-weighted and both DALYs and costs were discounted at an annual rate of 3%.

Data sources on effects

Main components of the mathematical model are demography, breast cancer epidemiology, stage distribution, case fatality rates and disability weights.

Demographic and epidemiological data were both derived from Global Burden of Disease (GBD) estimates of the WHO for India [3]. Information on stage distribution was adapted from Groot et al. [20].

Survival and relapse estimates for hormone therapies, i.e. tamoxifen, aromatase inhibitors (AIs) and switch therapy, in combination with chemotherapy, were based on calculations with Adjuvant! Online [22]. Survival and relapse estimates for trastuzumab (stage I-IV) and taxanes (stage I-III) were derived from Slamon et al. [23], Smith et al. [24] and the Early Breast Cancer Trialists' Collaborative Group [25], respectively. As AIs are associated with bone loss, biphosphonates, which prevent these side-effects, are added to the regimen, but do not have a significant effect on survival or relapse [26]. All drugs, except for trastuzumab, are assumed to have no significant effect on survival and relapse in stage IV [17]. All effects were eventually combined to calculate case fatality rates and relapse rates (Table 2). We assumed that stage specific disability weights are equal for all intervention scenarios and that all patients will have relapse to stage IV at a constant rate.

Table 2. *All 21 scenarios with stage specific case fatality rates, relapse rates and disability weights*

	Intervention scenario	Case fatality rates (10 years)				Relapse rates				Disability weights			
		Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV
0	Null scenario	0.01413	0.04655	0.11702	0.27567	0.02506	0.06710	0.15640	0.00000	0.068	0.071	0.073	0.090
1	CMF + tamoxifen	0.01110	0.02873	0.05454	0.27567	0.01341	0.03222	0.06135	0.00000	0.068	0.070	0.072	0.073
2	CMF + tamoxifen + AI + biphosphonates	0.01110	0.02873	0.05454	0.27567	0.01245	0.02997	0.05764	0.00000	0.068	0.070	0.072	0.073
3	CMF + tamoxifen + AI + biphosphonates	0.01110	0.02873	0.05454	0.27567	0.01245	0.02997	0.05764	0.00000	0.068	0.070	0.072	0.073
4	CAF + tamoxifen	0.01002	0.02432	0.04475	0.27567	0.01109	0.02706	0.05432	0.00000	0.068	0.070	0.072	0.073
5	CAF + tamoxifen + taxanes	0.00941	0.02315	0.04384	0.27567	0.01083	0.02556	0.05039	0.00000	0.068	0.070	0.072	0.073
6	CAF + tamoxifen + AI + biphosphonates	0.01002	0.02432	0.04475	0.27567	0.01033	0.02525	0.05063	0.00000	0.068	0.070	0.072	0.073
7	CAF + tamoxifen + switch therapy + biphosphonates	0.01002	0.02432	0.04475	0.27567	0.01033	0.02525	0.05063	0.00000	0.068	0.070	0.072	0.073
8	CAF + tamoxifen + AI + biphosphanates + taxanes	0.00941	0.02315	0.04384	0.27567	0.01007	0.02375	0.04681	0.0000	0.068	0.070	0.072	0.073
9	CAF + tamoxifen + switch therapy + biphosphonates + taxanes	0.00941	0.02315	0.04384	0.27567	0.01007	0.02375	0.04681	0.0000	0.068	0.070	0.072	0.073
10	AC + tamoxifen	0.01110	0.02873	0.05454	0.27567	0.01341	0.03222	0.06135	0.00000	0.068	0.070	0.072	0.073
11	AC+ tamoxifen + taxanes	0.01049	0.02756	0.05362	0.27567	0.01315	0.03071	0.05749	0.00000	0.068	0.070	0.072	0.073
12	AC + tamoxifen + AI + biphosphonates	0.01110	0.02873	0.05454	0.27567	0.01245	0.02997	0.05764	0.00000	0.068	0.070	0.072	0.073
13	AC + tamoxifen + switch therapy + biphosphanates	0.01110	0.02873	0.05454	0.27567	0.01245	0.02997	0.05764	0.00000	0.068	0.070	0.072	0.073
14	AC + tamoxifen + AI + biphosphonates + taxanes	0.01049	0.02756	0.05362	0.27567	0.01219	0.02846	0.05379	0.00000	0.068	0.070	0.072	0.073
15	AC + tamoxifen + switch therapy + biphosphonates + taxanes	0.01049	0.02756	0.05362	0.27567	0.01219	0.02846	0.05379	0.00000	0.068	0.070	0.072	0.073
16	AC + tamoxifen + trastuzumab	0.01033	0.02675	0.05077	0.25664	0.01341	0.03222	0.06135	0.00000	0.068	0.070	0.072	0.073
17	AC+ tamoxifen + taxanes + trastuzumab	0.00976	0.02566	0.04992	0.25664	0.01315	0.03071	0.05749	0.00000	0.068	0.070	0.072	0.073
18	AC + tamoxifen + AI + biphosphonates + trastuzumab	0.01033	0.02675	0.05077	0.25664	0.01245	0.02997	0.05764	0.00000	0.068	0.070	0.072	0.073
19	AC + tamoxifen + switch therapy + biphosphonates + trastuzumab	0.01033	0.02675	0.05077	0.25664	0.01245	0.02997	0.05764	0.00000	0.068	0.070	0.072	0.073

	Intervention scenario	Case fatality rates (10 years)				Relapse rates				Disability weights			
		Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV
20	AC + tamoxifen + AI + biphosphonates + taxanes + trastuzumab	0.00976	0.02566	0.04992	0.25664	0.01219	0.02846	0.05379	0.00000	0.068	0.070	0.072	0.073
21	AC + tamoxifen + switch therapy + biphosphonates + taxanes + trastuzumab	0.00976	0.02566	0.04992	0.25664	0.01219	0.02846	0.05379	0.00000	0.068	0.070	0.072	0.073

Chemotherapies: CMF consist of cyclophosphamide (PO), methotrexate and 5-fluorouracil (both IV), AC of cyclophosphamide and doxorubicin (both IV) and CAF of cyclophosphamide (PO), doxorubicin and 5-fluoracil. Dosages 18, 27: Cyclophosphamide PO 2.5 mg/kg bodyweight and IV 13.5 mg/kg bodyweight. Doxorubicin 1.8 mg/kg bodyweight. 5-fluorouracil 12 mg/kg bodyweight. Methotrexate 40 mg/m2 body surface. Tamoxifen 30 mg/day. Aromatase inhibitors; anastrozole 1 mg/day, letrozole 2.5 mg/day and exemestane 25 mg/day. Switch therapy (combination of tamoxifen and aromatase inhibitors) is dosed similarly. Start dosage for trastuzumab 4 mg/kg bodyweight, maintenance dosage 2 mg/kg. Taxanes; paclitaxel 90 mg/m2 body surface and docetaxel 175 mg/m2 body surface. Biphosphonates as a single dose of 4. We assumed the average height to be 1.66 meters, average weight 60 kg and body surface 1.62 m2.

Data on immunohistochemical characteristics of breast cancer patients (ER- and HER2 status), lymph node status and menopausal status were based on the literature [28-34]. Datasets on these characteristics were derived from multiple studies. All data were weighed for the sample size of the corresponding study and eventually combined to form the weighting factors (Table 3). These data were used to calculate the overall effect of each regimen on survival or relapse, since eligibility for drugs is determined by patients' immunohistochemical profile, nodal- and menopausal status (Table 2). Each separate effect of one drug was weighted for the percentage of patients who are eligible for these drugs within the regimen (e.g. the effect of scenario 1 is calculated by combining the effect of CMF, which all patients receive, with the effect of tamoxifen, which 52% of all patients receive).

We did not discriminate between the prescription of different types of AIs (i.e. anastrozole, letrozole and exemestane) and taxanes (i.e. paclitaxel and docetaxel) as they do not show a significant difference in effect on survival and relapse [22]. Therefore, we used the terms 'aromatase inhibitors' and 'taxanes' within the regimen, indicating all subtypes of the concerning drug.

Table 3. *Weighting factors for effects and costs*

Weighting factor	Stage	Value	Data sources
ER+	All stages	52.0% (default)	Ambroise et al. [28], Munjal et al. [32], Ghosh et al. [30] and Verma et al. [34]
HER2+	All stages	20.3% (default)	Ambroise et al. [28], Ghosh et al. [30], Kumar et al. [31] and Verma et al. [34]
Node+	I	25.0%	Tata Memorial Centre
	II	65.0%	
	III	100.0%	
	IV	90.0%	
Postmenopausal	All stages	63.9% (default)	Ambroise et al. [28], Gadgil et al. [29], Kumar et al. [31], Munjal et al. [32], Sandhu et al. [33] and Verma et al. [34]

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Data sources on costs

The costs of the chemotherapy regimens were derived from the Indian drug price index [35] and the literature [36, 37]. We also did not make a distinction between the prescription of different types of AIs and taxanes to calculate the costs. To calculate the unit costs for systemic treatment of each regimen (all stages), costs were weighted for patients' eligibility for drugs and we used the same allocation rules as explained before for calculating the effects (Table 4).

Total unit costs for breast cancer diagnosis, treatment (except for systemic therapy) and follow-up derived from standard WHO-CHOICE database and corrected for inflation to 2011 (Table 4) [3, 38]. All drug costs were estimated in 2013 Indian Rupees and converted to US dollars (US$) using a currency exchange rate of 1US$:59.53 Indian Rupees (2013).

Cost-effectiveness analysis

Average cost-effectiveness ratios (ACERs) were calculated for each intervention by dividing the total costs by the total of effects. To assess the expansion path, defined as the order in which interventions should be chosen according to their incremental cost-effectiveness ratio (ICER), we calculated the ICERs of each intervention by dividing incremental costs of each intervention by their incremental health effects. Solely interventions that are both more effective and less costly in comparison to other scenarios are included in the expansion path.

Results of CEA should be interpreted according to a certain cost-effectiveness threshold. The WHO-CHOICE defines an intervention as very cost-effective when the costs of one DALY averted are less than the gross domestic product (GDP) per capita and cost-effective when these costs are below 3 times GDP per capita [15]. The GDP per capita in Maharashtra was 1,681 US$ in 2012, resulting in a threshold value for interventions of 5,044 US$ per DALY averted.

Table 4. *Average utilisation of diagnosis and treatment services and unit costs per patient*

Procedure	Ingredients	Stage I	Stage II	Stage III	Stage IV	Relapse	Unit costs per patient (US$)
Initial diagnosis and lab tests		1	1.1	2.1	1.8	0.7	166.42
Radiotherapy	Radiotherapy planning	0.4	0.3	1.0	0.1	0.6	21,16
	Radiotherapy	0.4†	0.3†	1.0†	0.1†	0.6†	2,12 (per fraction)
Surgery	Partial mastectomy	0.4	0.3	0.1	0	0	180.35
	Modified radical mastectomy	0.6	0.7	0.9	0.05	0.05	183.96
	General anaesthesia	1	1	1	0.05	0.05	42.95
	Hospitalization days for surgery	2	2	6	6	6	12.83
Chemotherapy	CMF/AC/CAF	1	1	1	1	1	457.93 / 170.13 / 819.75‡
	Taxanes	25.0%	65.0%	100.0%	90.0%	90.0%	1,008.50
	Trastuzumab	20.3%	20.3%	20.3%	20.3%	20.3%	29,865.71‡
Endocrine therapy	Tamoxifen	52.0 / 18.8%*	52.0 / 18.8%*	52.0 / 18.8%*	52.0 / 18.8%*	52.0 / 18.8%*	554.49 (5 years)
	Aromatase inhibitors	33.2%*	33.2%*	33.2%*	33.2%*	33.2%*	1,367.28 (5 years)
	Switch therapy	33.2%*	33.2%*	33.2%*	33.2%*	33.2%*	960.88 (5 years)
Additional drugs	Biphosphonates	33.2%*	33.2%*	33.2%*	100%**	100%**	45.27

† Radiotherapy for stage I is given in 10 fractions, stage II in 7.5 fractions, stage III in 25 fractions, stage IV in 25 fractions and for relapse in 15 fractions (2 Gy, by linear accelerator).

‡ Costs for intravenous administration of the drug are included

** If an intervention scenario only includes the hormone therapy tamoxifen, the effect and costs of tamoxifen were only weighted for the patients who are ER-positive, and therefore eligible for tamoxifen (i.e. 52.0%). If a scenario also includes aromatase inhibitors or switch therapy, we made the distinction between patients who are eligible for tamoxifen (premenopausal, 36.1%) and eligible for aromatase inhibitors/switch therapy (postmenopausal, 63.9%). We assumed that all patients who are ER+ and premenopausal receive tamoxifen and all patients who are ER+ and postmenopausal receive AIs or switch therapy.*

*** All patients in stage 4 and those with relapse receive bisphosphonates, regardless if they receive AIs/switch therapy or not.*

Sensitivity analysis

We performed a deterministic one-way sensitivity analysis to assess the impact of drug prices on the results of the cost-effectiveness analysis by varying their price values. Input values on drug prices were varied using average, minimal and maximal prices, derived from the national price index [35] and other literature [36, 37].

Results

Results on annual costs, effects (DALYs averted per year) and cost-effectiveness for three different drug price levels are shown in table 5 and graphically in figure 2. All 21 scenarios also include the diagnosis, treatment and follow-up for breast cancer stages I to IV, as described by Zelle et al. [19]. Programme and training costs were kept at the same level for all scenarios.

Annual total costs for treatment, including only chemotherapy and any type of hormone therapy (i.e. tamoxifen, aromatase inhibitors or switch therapy) vary from 416 million to 689 million US$, with treatment scenarios including AIs being the most expensive. Adding taxanes to these regimens leads to annual total treatment costs that range between 675 million to 943 million US$. Treatment scenarios including trastuzumab (with or without taxanes) are the most expensive, as the total treatment costs vary from 2.2 billion to 2.5 billion US$ per year.

Intervention scenarios consisting of CAF, hormone therapy and taxanes avert the most DALYs per year, i.e. 268,173. AC combined with hormone therapy and taxanes averts less DALYs per year; 230,981. Intervention scenarios including only chemotherapy and hormone therapy avert 225,912 (CMF and AC) to 262,776 (CAF) DALYs per year. The amount of DALYs averted per year by regimens including AC, hormone therapy, trastuzumab (and taxanes) avert 243,238 and 248,088 DALYs per year, respectively.

The average cost-effectiveness ratios (ACERs) of intervention scenarios which include chemotherapy and hormone therapy vary from 1,840 to 2,624 US$ per DALY averted. Adding taxanes leads to slightly higher ACERs, i.e. 2,924 to 3,516 US$ per DALY averted. Cost-effectiveness ratios of treatment scenarios increase even more when including trastuzumab (and taxanes); these ACERs vary from 9,143 to 10,272 US$ per DALY averted respectively.

Figure 2 shows the expansion path, i.e. the order in which interventions should be implemented according to their ICER. The upper line represents the cost-effectiveness threshold of three times GDP per capita per DALY averted, the lower line one time GDP per capita per DALY. When comparing all interventions to the null-scenario, AC combined with tamoxifen is the most cost-effective and costs 1,840 US$ per DALY averted. The next best scenario to implement is CAF combined with tamoxifen (ICER = 5,102 US$ per DALY averted), followed by CAF combined with tamoxifen and taxanes (ICER = 47,343 US$ per DALY averted).

According to the set threshold value of 3x GDP per capita per DALY averted (i.e. 5,044 US$ per DALY averted), only AC combined with tamoxifen can be considered cost-effective. However, the ICER of CAF combined with tamoxifen is only slightly higher than this cut-off point and could still be recommended if this threshold is not strictly interpreted. When using the average drug prices, all other intervention scenarios (i.e. all scenarios including CMF, CAF combined with AIs or switch therapy, and scenarios including AC combined with AIs, switch therapy, taxanes and/or trastuzumab) are dominated. Nevertheless, these interventions could still be considered based on criteria other than cost-effectiveness. Moreover, CMF combined with tamoxifen could be the most cost-effective if lower drugs prices are used. Intervention scenarios that include trastuzumab cannot be considered cost-effective (ICERs vary from 9,143 to 10,272).

We investigated how much the price of trastuzumab should decline to be included in the expansion path, i.e. to become cost-effective and considered for implementation. When the price of trastuzumab is 50 times lower than its original price of approximately 30,000 US$ per patient per year, intervention scenarios including trastuzumab become cost-effective. After lowering the price of trastuzumab to circa 590 US$, the first intervention that should be implemented according to the expansion path is AC combined with tamoxifen, followed by AC combined with tamoxifen and trastuzumab (ICER is 2,916 US$ per DALY averted). Interventions scenarios consisting of AC, hormone therapy, trastuzumab and taxanes are dominated by CAF combined with tamoxifen and CAF in combination with tamoxifen and taxanes, the third and fourth best option, respectively.

Sensitivity analysis

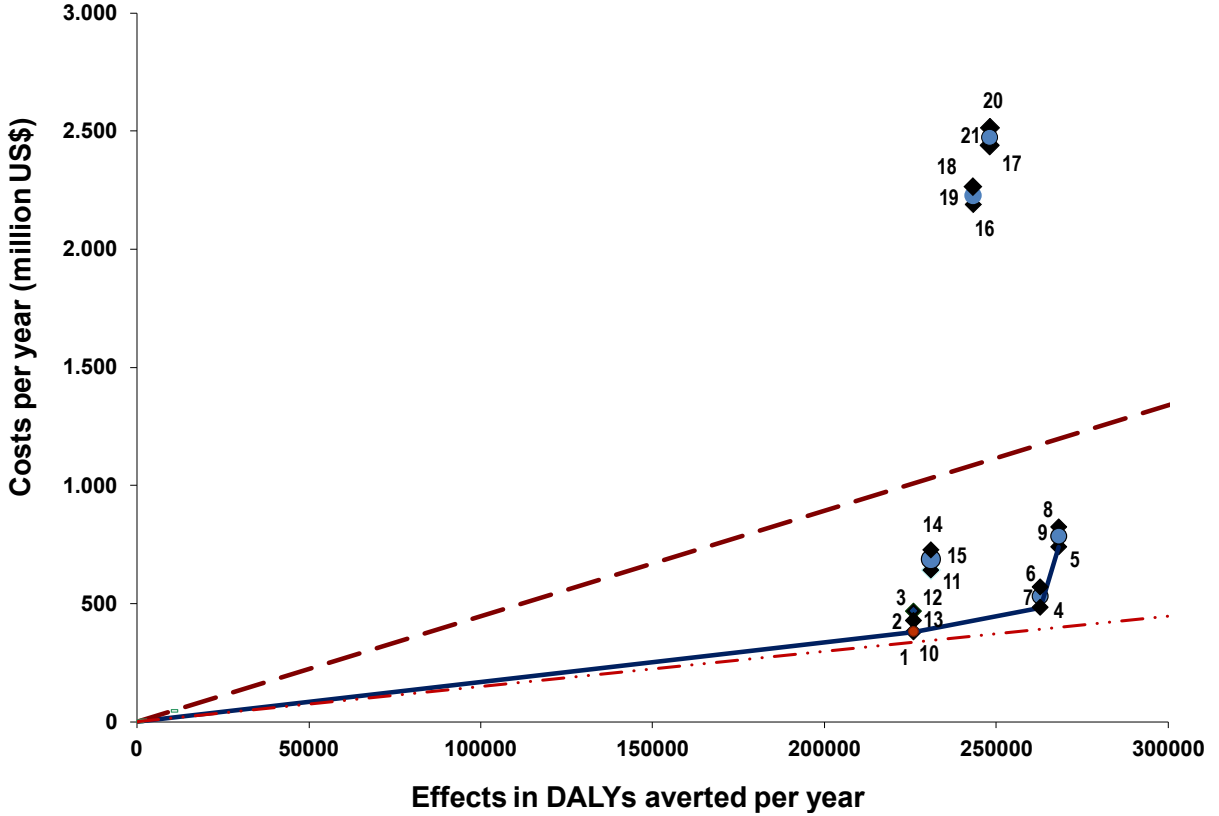
We explored the impact of different prices for drugs for systemic treatment on cost-effectiveness by using average prices, minimum and maximum prices. This analysis showed that our outcomes and conclusions change when using different prices. When using average and maximum prices, AC combined with tamoxifen is most cost-effective, followed by CAF combined with tamoxifen and CAF in combination with tamoxifen and taxanes. However, as Table 5 shows, when using minimum prices, CMF combined with tamoxifen is the most cost-effective (incremental CER is 1,406 US$ per DALY averted), dominating AC combined with tamoxifen. The second best option to implement is CAF with tamoxifen, followed by CAF combined with tamoxifen and taxanes.

Table 5. *Annual patient and total costs (US$), effectiveness (DALYs averted per year), cost-effectiveness ratios using average, minimum and maximum prices per scenario for systemic therapy as a part of breast cancer treatment in Maharashtra, India*

	Intervention scenario	Annual patient costs (US$) [a]	Annual total costs (US$) [a]	Effectiveness (DALYs averted per year) [b]	ACER (average prices) [c]	ICER (average prices) [d]	ICER (minimum prices) [d]	ICER (maximum prices) [d]
1	CMF + tamoxifen	465,744,621	500,637,748	225,912	2,216	Dominated	1,406	Dominated
2	CMF + tamoxifen + AI + biphosphanates	552,984,203	587,877,329	225,912	2,602	Dominated	Dominated	Dominated
3	CMF + tamoxifen + AI + biphosphanates	513,237,542	548,130,668	225,912	2,426	Dominated	Dominated	Dominated
4	CAF + tamoxifen	568,839,951	603,733,077	262,776	2,298	5,102	2,372	8,427
5	CAF + tamoxifen + taxanes	824,374,849	859,267,975	268,173	3,204	47,343	38,441	58,664
6	CAF + tamoxifen + AI + biphosphanates	654,502,251	689,395,377	262,776	2,624	Dominated	Dominated	Dominated
7	CAF + tamoxifen + switch therapy + biphosphanates	615,210,426	650,103,552	262,776	2,474	Dominated	Dominated	Dominated
8	CAF + tamoxifen + AI + biphosphanates + taxanes	908,009,448	942,902,574	268,173	3,516	Dominated	Dominated	Dominated
9	CAF + tamoxifen + switch therapy + biphosphanates + taxanes	868,944,773	903,837,899	268,173	3,370	Dominated	Dominated	Dominated
10	AC + tamoxifen	380,756,145	415,649,271	225,912	1,840	1,840	Dominated	3,276
11	AC+ tamoxifen + taxanes	640,521,721	675,414,847	230,981	2,924	Dominated	Dominated	Dominated
12	AC + tamoxifen + AI + biphosphanates	468,501,068	503,394,194	225,912	2,228	Dominated	Dominated	Dominated
13	AC + tamoxifen + switch therapy + biphosphanates	428,754,407	463,647,533	225,912	2,052	Dominated	Dominated	Dominated
14	AC + tamoxifen + AI + biphosphanates + taxanes	726,140,842	761,033,968	230,981	3,295	Dominated	Dominated	Dominated
15	AC + tamoxifen + switch therapy + biphosphanates + taxanes	686,622,874	721,516,000	230,981	3,124	Dominated	Dominated	Dominated
16	AC + tamoxifen + trastuzumab	2189,077,647	2,223,970,773	243,238	9,143	Dominated	Dominated	Dominated
17	AC + tamoxifen + taxanes + trastuzumab	2438,474,224	2,473,367,350	248,088	9,970	Dominated	Dominated	Dominated
18	AC + tamoxifen + AI + biphosphanates + trastuzumab	2266,074,173	2,300,967,300	243,238	9,460	Dominated	Dominated	Dominated
19	AC + tamoxifen + switch therapy + biphosphanates + trastuzumab	2,226,325,788	2,261,218,914	243,238	9,296	Dominated	Dominated	Dominated
20	AC + tamoxifen + AI + biphosphanates + taxanes + trastuzumab	2,513,381,586	2,548,274,712	248,088	10,272	Dominated	Dominated	Dominated
21	AC + tamoxifen + switch therapy + biphosphanates + taxanes + trastuzumab	2,473,861,917	2,508,755,043	248,088	10,112	Dominated	Dominated	Dominated

*[a] Costs in this table are in 2013 US$ (1 INR = 0,01679 US$); [b] DALYs, disability-adjusted life-years (age weighted, discounted); [c] **ACER**= Average cost-effectiveness ratio compared to the do nothing-scenario (US$ per DALY averted). [d] **ICER** = Incremental cost effectiveness ratio, ratio of additional cost per additional life-year saved when next intervention is added to a mix on the intervention path (additional US$ per additional DALY saved).*

***Figure 2**. Expansion path of systemic drug interventions according to their incremental cost-effectiveness*



The threshold values are based on the gross domestic product (GDP) of Maharashtra in 2012 [41, 42]. The upper dotted line represents the threshold value of 3 times GDP per capita per disability adjusted life year (DALY) averted (5,044 US$ per DALY averted). The lower dotted line represents a value of 1 times GDP per capita per disability adjusted life year (DALY) averted (1,681 US$ per DALY averted).

Discussion

We have investigated the cost-effectiveness of several interventions for breast cancer treatment in India and focussed on the impact of systemic drug treatment on cost-effectiveness. This is the first article to provide economic evidence on the cost-effectiveness of breast cancer treatment, and the impact of systemic therapy on this cost-effectiveness, in India. Our results show that AC combined with tamoxifen is most cost-effective intervention costing 415 million US$ (ICER 1,840 per DALY averted). CAF together with tamoxifen is the second most cost-effective intervention and CAF in combination with tamoxifen and taxanes the third best option when assuming average prices. Trastuzumab is not cost-effective and prices need to be approximately 50 times lower to be considered cost-effective.

Our analyses show that the treatment scenario AC combined with tamoxifen is the most cost-effective and costs 1,840 US$ per DALY averted, which is below the threshold value of 5,044 US$ per DALY averted. Other treatment scenarios including AC or CMF combined with any type of hormone therapy (tamoxifen, AIs or switch therapy), all have the same effect on survival and/or relapse, but are slightly more costly and therefore dominated on the expansion path. However, as these small differences are likely not clinically and policy relevant and the selection of specific therapies depends on patient preferences and patient characteristics, we recommend all intervention scenarios that include AC or CMF combined with any type of hormone therapy for implementation in India.

The second best option according to the expansion path is CAF combined with tamoxifen ($5,102 per DALY averted). This value is slightly higher than the threshold value of 3 times GDP per capita, but nevertheless can be considered for implementation if sufficient resources are available in India. If even more resources are available in India, CAF combined with AIs or switch therapy might also be considered for implementation. Intervention scenarios consisting of CAF and AIs or switch therapy have the same health effects as CAF combined with tamoxifen, but have higher total costs (85.7 million US$ and 46.4 million US$ extra per year respectively) and relatively higher ICERs ($7,426 and $6,360 per DALY averted respectively).

The third best option, CAF combined with tamoxifen and taxanes costs $47,343 per DALY averted. This value exceeds the threshold value and therefore, CAF in combination with tamoxifen and taxanes cannot be considered cost-effective. Comparable interventions with taxanes, CAF combined with AIs or switch therapy and taxanes, are also not cost-effective, as they have even higher ICERs. All scenarios including AC, hormone therapy and taxanes are dominated and therefore also not recommended for implementation.

As our results indicate, intervention scenarios including trastuzumab are not cost-effective despite the results of other studies, showing that regimens including trastuzumab are cost-effective [39, 40]. However, these studies are mostly conducted in developed countries, where the threshold values, defined by 3 times GDP per capita or willingness to pay (WTP), lies much higher. The GDP per capita in a developing country such as India is quite low in comparison to most developed countries and therefore, when the WHO-CHOICE methodology is applied, the GDP limits interventions to be considered cost-effective. Moreover, trastuzumab is supplied by Western companies, with western prices, and are thus very expensive in comparison to other drugs, that are produced by generic drug manufacturers in India for much lower prices. Our analysis showed that the price of trastuzumab needs to be 50 times lower to be considered cost-effective in Maharashtra, India. Achieving these price reductions could be considered by the Indian government, as it is able to influence the drug market through policy making. Reduced trastuzumab prices could improve access and therefore the scope of breast cancer treatment, since approximately 20% of all female breast cancer patients are eligible for trastuzumab.
Our sensitivity analysis showed that the order of the expansion path changes when varying drug prices between minimum, average and maximum prices. AC combined with tamoxifen was most-cost-effective using average and maximum prices, however, when using minimum prices CMF combined with tamoxifen is the most cost-effective. This can be explained by the price ranges of AC and CMF. AC has a much smaller price range and a minimum price of approximately 28 US$ compared to CMF, which has a minimum price of circa 3 US$. As this analysis shows that the outcome of our CEA is sensitive to different assumptions on drug prices, and therefore influences the choice of selecting the most cost-effective intervention, it seems important for the Indian government to apply drugs with the lowest prices, while maintaining quality.

There are some limitations of our study. First, demographic and epidemiological data and data on stage distribution were derived from WHO and UN datasets specific for India and from 2005, and therefore do not entirely represent the current population of Maharashtra.

Second, calculations for effects were based on using Adjuvant! Online. As this program makes several assumptions on the effectiveness and the difference in effectiveness between several types of chemotherapy and hormone therapy, correct administration of drugs and the best possible surgery and radiotherapy, the used effectiveness estimates might not represent the actual effectiveness of these therapies. Also, we did not perform sensitivity analysis to investigate whether our model is sensitive to alternative assumptions on effectiveness.

Third, data on nodal status per stage were adapted from expert opinion and probably do not represent the entire population in Maharashtra. Data on other eligibility factors, i.e. HER2-, ER- and menopausal status were derived from literature. Some studies had a considerably small sample size, and more importantly, these data was not stage specific. Different distribution could influence the overall effect of an intervention and total patient costs due to different percentages of eligibility.

Fourth, we did not discriminate between the prescription of different types of taxanes (i.e. paclitaxel and docetaxel) and AIs (i.e. anastrozole, letrozole and exemestane) and used averaged prices. However, in reality, not all types might be available or some types might be prescribed more often than others. These variations could influence the unit costs per patients, as some types are more expensive than others (e.g. docetaxel is more expensive than paclitaxel).

Fifth, input data on GDP per capita was available until 2012 and data on the GDP per capita in PPP and the PPP exchange rate was available until 2011. Moreover, for non-drug costs, we were only able to correct for inflation from 2000 to 2012. However, we used drug prices from 2013 and these discrepancies could have led to relatively high drug costs compared to for example GDP per capita, resulting in an overestimation of costs.

Sixth, as stated before, out-of-pocket expenditure on health care is very high in India (59%). The impact of this financial burden might be stronger in some subpopulations, and consequently might have high impact on the access and adherence to treatment and the degree of benefit from breast cancer treatment. However, we performed our analyses from a health care perspective, and therefore did not include opportunity costs and travel costs for patients. Analysis from a societal perspective could give a more detailed evaluation of the cost-effectiveness of breast cancer treatment and the financial burden for specific subpopulations, and for this reason lead to more targeted policy.

Seventh, all interventions were modelled at a geographical coverage level of 95%. In reality, however, these high levels of population and treatment coverage are not reached in India due to barriers in access and compliance and this could have led to a general overestimation of both effects and costs. However, the above limitations fall within the aim of WHO-CHOICE to provide generalized and comparable cost-effectiveness estimates of public health strategies.

Despite these limitations, we can conclude that treatment consisting of AC or CMF combined with hormone therapy can be considered cost-effective in India according to WHO-CHOICE standardised methods. When more resources become available for breast cancer control in India, CAF combined with hormone therapy could be considered for implementation as their ICERs are slightly above the threshold value. However, cost-effectiveness should not be the only criterion for decisions on breast cancer treatment and decisions should also depend on patients' characteristics and preferences. Treatment scenarios that include taxanes are generally not considered cost-effective because their ICERs are above the proposed threshold value and therefore not recommended. Treatments comprising trastuzumab are also not cost-effective and trastuzumab prices should be 50 fold lower to be considered cost-effective.

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7

CHAPTER

Cost, effects and cost-effectiveness of strategies to combat breast, cervical and colorectal cancer in Sub-Saharan Africa and Southeast Asia

a mathematical modelling study

Knowledge comes, but wisdom lingers.

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Abstract

Objective
To determine the costs and health effects of interventions to combat breast, cervical and colorectal cancers in order to guide resource allocation decisions in developing countries.

Setting
Two sub-regions of the world: countries in Sub-Saharan Africa with very high adult and high child mortality; and countries in Southeast Asia with high adult and high child mortality.

Design
Cost-effectiveness analysis of prevention and treatment strategies for breast, cervical and colorectal cancer, using mathematical modelling based on a lifetime population model.

Data sources
Demographic and epidemiological data were taken from the WHO mortality and global burden of disease databases. Estimates of intervention coverage, effectiveness and resource needs were based on clinical trials, treatment guidelines and expert opinion. Unit costs were taken from the WHO-CHOICE price database.

Main outcome measures
Cost per disability adjusted life year (DALY) averted, expressed in international dollars (I$) for the year 2005.

Results
In both regions, certain interventions in cervical cancer control (i.e. screening through Pap smears or visual inspection with acetic acid (VIA) in combination with treatment) and colorectal cancer control (i.e. increasing the coverage of treatment interventions) cost less than I$ 2,000 per DALY averted and can be considered highly cost-effective. In the Sub-Saharan African, screening for colorectal cancer (i.e. by colonoscopy at age 50 in combination with treatment) costs between IS2,000 and I$ 6,000 per DALY averted and can be considered cost-effective. In both regions, certain interventions in breast cancer control (treatment of all stages in combination with mammography screening) cost between I$ 2,000 and I$ 6,000 per DALY averted and can also be considered cost-effective. Other interventions, such as fruit and vegetable campaigns or subsidies in colorectal cancer control, are not cost-effective according to the criteria defined.

Conclusion
A number of highly cost-effective interventions to combat cervical and colorectal cancer are available in the African and Asian sub-regions. In cervical cancer control, these include screening through Pap smear or VIA, in combination with treatment. In colorectal cancer, increasing treatment coverage is highly cost-effective (screening through colonoscopy is cost-effective in the African sub-region). In breast cancer control, mammography screening in combination with treatment of all stages is cost-effective.

Keywords
Cost-Utility Analysis, Breast Cancer, Cervical Cancer, Colorectal cancer.

Introduction

Malignant neoplasms are responsible for nearly 7.5 million deaths, representing some 13% of all mortality and 5% of the global burden of disease in terms of DALYs lost [1]. Leading contributors to global cancer mortality include tracheal, bronchial and lung cancer (18%), stomach cancer (11%), colorectal cancer (9%), liver cancer (8%), breast cancer (7%), oesophageal cancer (7%), lymphomas (5%), oral cancers (5%), prostate cancer (4%), leukaemia (4%), pancreatic cancer (4%) and cervical cancer (4%) [1].

This study evaluates a set of 240 interventions (and intervention combinations) for prevention, screening and treatment in breast, cervical and colorectal cancer control. The cost-effectiveness of interventions against tracheal, bronchial and lung cancer in the context of tobacco use is presented in a companion article in this series [2].The study does not evaluate interventions for stomach cancer due to the absence of known efficacious interventions. Likewise, it does not evaluate interventions against liver cancer: although preventive interventions exist, only part of their impact is captured by reductions in liver cancer (Hepatitis B vaccination has a more direct impact on hepatitis B and cirrhosis, and interventions to reduce alcohol use are considered within the context of neuropsychiatric conditions in this series [3]).

Breast cancer incidence varies considerably between world regions, incidence rates can be up to eight times higher in high-income than in low-income regions, such as South-Asia [1]. Similarly, colorectal cancer incidence rates are five to ten times higher in high-income compared to low-income regions. Conversely, the burden of cervical cancer is inversely related to economic development, with 300-400 disability-adjusted life years (DALYs) per million people in high-income regions, rising to 800-1,250 in low-income regions [1].

This paper provides indications on the cost-effectiveness of prevention, screening and treatment strategies for reducing the burden associated with leading causes of cancer in developing countries. It draws on previously undertaken analyses of each of the three selected cancers [4-6], here updated to the year 2005 and brought together in order to elicit key insights into the comparative costs and effects of different intervention strategies across and beyond individual cancer entities. In common with other papers in this series, we evaluated interventions for two major global regions using a standardized analytical approach. The two regions are referred to as Sub-Saharan Africa, including those African countries with very high adult and high child mortality (referred to as Afr-E in the WHO classification) and Southeast Asia including those countries in Asia with high adult and high child mortality (referred to as Sear-D). The use of the standardized WHO-CHOICE framework allows the comparison of the cost-effectiveness of interventions within cancer control, but also in a broader respect with intervention in non-communicable disease control as presented in this series, and with interventions on infant and infectious diseases as reported earlier [7].

Table 1. *Epidemiology of breast, cervical, and colorectal cancer in WHO sub-Saharan African sub-region AfrE and South East Asian sub-region SearD**

Age group (years)	African region Afr-E				South-East Asian region Sear-D			
	Breast cancer (women)	Cervical cancer (women)	Colorectal cancer		Breast cancer (women)	Cervical cancer (women)	Colorectal cancer	
			Men	Women			Men	Women
Incidence (per 1000 population)								
15–29	0.02	0.23	0.02	0.00	0.01	0.18	0.01	0.00
30–44	0.38	0.27	0.05	0.04	0.21	0.12	0.02	0.02
45–59	0.82	1.58	0.31	0.20	0.45	0.75	0.12	0.09
60–69	1.79	3.46	0.91	0.49	0.79	1.21	0.35	0.23
70–79	2.44	3.95	1.59	0.83	0.95	0.99	0.42	0.30
≥80	3.01	3.56	3.36	1.61	2.18	1.61	0.83	0.89
Prevalence (per 1000 population)								
15–29	0.07	0.08	0.07	0.02	0.18	8.44	0.11	0.11
30–44	1.44	0.76	0.20	0.12	2.40	3.29	0.24	0.43
45–59	3.03	3.83	0.89	0.45	3.43	11.00	0.81	0.87
60–69	6.43	7.45	3.50	1.55	3.48	9.32	2.14	1.46
70–79	7.60	5.72	5.16	2.08	2.28	2.85	1.40	1.15
≥80	8.60	4.26	9.48	3.48	3.58	2.63	1.50	1.68
Mortality (per 1000 population)								
15–29	0.01	0.05	0.01	0.00	0.00	0.03	0.00	0.00
30–44	0.13	0.09	0.05	0.02	0.07	0.04	0.02	0.01
45–59	0.47	0.69	0.13	0.07	0.28	0.33	0.04	0.03
60–69	1.26	2.27	0.41	0.26	0.65	0.84	0.20	0.12
70–79	2.04	3.61	1.23	0.58	0.85	1.93	0.32	0.21
≥80	3.01	3.55	3.20	1.44	2.18	1.61	0.78	0.80

**Data source: WHO Global Burden of Disease [1].*

Methods

This section outlines the main principles of WHO-CHOICE analysis, and its application to the cost-effectiveness analysis of breast, cervical and colorectal control. Further details on WHO-CHOICE are presented in detail in the General Appendix A and other documents [8,9]. Details on the disease-specific analysis are reported in Appendices 1-3.

Intervention effects

WHO-CHOICE employs an epidemiological, population-based approach to the assessment of health outcomes. Along with background demographic rates, observed rates of cancer incidence, prevalence, remission and case-fatality (Table 1) - primarily drawn from the global burden of disease database 1 - are represented as parameters in a state-transition model in order to establish the total number of years of healthy life experienced over the lifetime of a defined population (see General Appendix A, [8,9]). The model is successively run for each intervention scenario and compared to the baseline of no interventions for the disease in question. Thus, the health effects of a range of preventive, screening and treatment strategies for cancer are considered, with effectiveness expressed as a reduction in epidemiological rates such as incidence or case-fatality. We followed standardized WHO-CHOICE methodology to the identification of best available evidence on the (clinical or population) effectiveness of interventions – in the ideal case, this evidence is retrieved from systematic reviews. In other instances, evidence is based on individual studies. In the extreme case where no evidence is available, estimates are based on expert opinion. We used evidence on intervention effectiveness pertaining to the regions under study, or extrapolated this from western settings where meaningful. Evaluated interventions are listed in Table 2 and their data sources for intervention effectiveness in Tables 3-5. DALYs averted were discounted at 3% per annum and age-weighted. Interventions were analyzed at WHO-CHOICE standardized geographic coverage levels of 50%, 80%, and 95%, referring to the percentage of eligible cases receiving treatment.For breast cancer, we evaluated lumpectomy with auxiliary dissection supplemented with external radiotherapy to the breast for stage I and II breast cancer. For stage III breast cancer, we evaluated neo-adjuvant chemotherapy followed by mastectomy with auxiliary dissection supplemented with adjuvant chemotherapy including external breast radiotherapy. For stage IV breast cancer, we evaluated systemic chemotherapy. All interventions include endocrine therapy for eligible patients. We also considered combinations of treatment strategies, both with and without the implementation of a breast awareness program and early case finding through biannual mammography screening in women age 50–70 years. Details on assumptions on intervention effectiveness are provided in Table 3, whereas the modeling design is provided in Appendix 1.

Table 2. *Evaluated interventions for breast, cervical, and colorectal cancer control in WHO sub-Saharan African sub-region AfrE and South East Asian sub-region SearD. All interventions were evaluated at 50%, 80%, and 95% coverage*

Intervention	Abbreviation
Breast cancer	
1: Stage I treatment (Lumpectomy with auxiliary dissection supplemented with external radiotherapy to breast. Eligible patients also receive endocrine therapy)	Stage I treatment
2: Stage II treatment (Lumpectomy with auxiliary dissection supplemented with external radiotherapy to breast. Eligible patients also receive endocrine therapy)	Stage II treatment
3: Stage III treatment (neo-adjuvant chemotherapy followed by mastectomy with auxiliary dissection supplemented with adjuvant chemotherapy. External radiotherapy to the breast. Eligible patients receive endocrine therapy)	Stage III treatment
4: Stage IV treatment (systemic chemotherapy supplemented with endocrine therapy for eligible patients)	Stage IV treatment
5: Combination treatment (treatment of all stages)	Combination treatment
6: Optimal programme (treatment of all stages plus biannual mammographic screening in women aged 50–70 years)	Optimal programme
Colorectal cancer	
1: Annual faecal occult blood tests	FOB1
2: Biennial faecal occult blood tests	FOB2
3: Sigmoidoscopy every 5 years	SIG5
4: Colonoscopy every 10 years	COL10
5: Annual faecal occult blood test + sigmoidoscopy every 5 years	FOB1SIG5
6: Faecal occult blood test at age 50 years	FOB50
7: Sigmoidoscopy at age 50	SIG50
8: Colonoscopy at age 50	COL50
9: Faecal occult blood test + sigmoidoscopy at age 50	FOBSIG50
10: Medical treatment of cancers	RX
11: Annual faecal occult blood tests + medical treatment	FOB1RX
12: Biennial faecal occult blood tests + medical treatment	FOB2RX
13: Sigmoidoscopy every 5 years + medical treatment	SIG5RX
14: Colonoscopy every 10 years + medical treatment	COL10RX
15: Annual faecal occult blood test + sigmoidoscopy every 5 years + medical treatment	FOB1SIG5RX
16: Faecal occult blood test at age 50 + medical treatment	FOB50RX
17: Sigmoidoscopy at age 50 + medical treatment	SIG50RX
18: Colonoscopy at age 50 + medical treatment	COL50RX
19: Faecal occult blood test + sigmoidoscopy at age 50 + medical treatment	FOBSIG50RX
20: Fruit and vegetables campaign	FVCAMP
21: Fruit and vegetables campaign + medical treatment	FVCAMPRX
22: Annual digital rectal examination	DRE1
23: Annual digital rectal examination + medical treatment	DRE1RX

Intervention	Abbreviation
Cervical cancer	
1: Annual screening by cervical smear test for ages 20–65 years (with removal of lesions)	Pap (1,20,65)*
2: Triennial screening by cervical smear test for ages 20–65 (with removal of lesions)	Pap (3,20,65)*
3: Screening by visual inspection with acetic acid at age 40 years (with removal of lesions)	VIA (40)*
4: Treatment of invasive cancer (including chemotherapy, radiotherapy, and/or surgery)	Rx
5: Annual smear test for ages 20–65 years + cancer treatment	Pap (1,20,65)* + Rx
6: Triennial smear test for ages 20–65 years + cancer treatment	Pap (3,20,65)* + Rx
7: Visual inspection with acetic acid at age 40 + cancer treatment	VIA (40)* + Rx
8: Screening by smear test every five years for ages 20–65 (with removal of lesions)	Pap (5,20,65)*
9: Smear test every five years for ages 20–65 + cancer treatment	Pap (5,20,65)* + Rx
10: Annual screening by smear test for ages 20–30 years, then annual smear test with HPV vaccination for ages 30–65 years	Pap (1,20,30) then Pap & HPV (1,30,65)
11: Annual smear test for ages 20–30 then annual smear test with HPV vaccination for ages 30–65 + cancer treatment	Pap (1,20,30) then Pap & HPV (1,30,65) + Rx
12: Triennial smear test for ages 20–30 then triennial smear test with HPV vaccination for ages 30–65	Pap (3,20,30) then Pap & HPV (3,30,65)
13: Triennial smear test for ages 20–30 then triennial smear test with HPV vaccination for ages 30–65 + cancer treatment	Pap (3,20,30) then Pap & HPV (3,30,65) + Rx
14: Smear test every five years for ages 20–30 then smear test with HPV vaccination every five years for ages 30–65	Pap (5,20,30) then Pap & HPV (5,30,65)
15: Smear test every five years for ages 20–30 then smear test with HPV vaccination every five years for ages 30–65 + cancer treatment	Pap (5,20,30) then Pap & HPV (5,30,65) + Rx
16: Screening by smear test at ages 35, 40, and 45 years (with removal of lesions)	Pap (35,40,45)*.
17: Smear test at ages 35, 40, and 45 + cancer treatment	Pap (35,40,45)* + Rx.
18: HPV vaccination at ages 35, 40, and 45 years (with removal of lesions)	HPV (35,40,45) *.
19: HPV vaccination at ages 35, 40, and 45 + cancer treatment	HPV (35,40,45) * + Rx
20: Screening by visual inspection with acetic acid at ages 35, 40, and 45 years	VIA (35,40,45)
21: Visual inspection with acetic acid at ages 35, 40, and 45 + cancer treatment	VIA (35,40,45) * + Rx
22: Screening by smear test at age 40 years (with removal of lesions)	Pap (40) *
23: Smear test at age 40 + cancer treatment	Pap (40) * + Rx
24: HPV vaccination at age 40 (with removal of lesions)	HPV (40) *
25: HPV vaccination at age 40 + cancer treatment	HPV (40) * + Rx
26: HPV vaccinations starting at age 12 at cost of US$0.60 per vaccine	HPVAC(12), $0.60/dose
27: HPV vaccinations starting at age 12 at US$0.60 + cancer treatment	HPVAC (12), $0.60/ dose + Rx
28: HPV vaccinations starting at age 12 at cost of US$2.00 per vaccine	HPVAC (12), $2.00/ dose
29: HPV vaccinations starting at age 12 at US$2.00 + cancer treatment	HPVAC (12), $2.00/ dose + Rx
30: Annual smear test for ages 20–65 years + HPV vaccinations starting at age 12 at cost US$0.60	Pap(1,20,65)*+HPVAC (12,$.60)
31: Triennial smear test for ages 20–65 years + HPV vaccinations starting at age 12 at cost US$0.60	Pap(3,20,65)*+HPVAC (12,$.60)
32: Visual inspection with acetic acid at age 40 + HPV vaccinations starting at age 12 at cost US$0.60	VIA(40)*+HPVAC (12), $.60)
33: Annual smear test for ages 20–65 years + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	Pap(1,20,65)*+HPVAC (12, $.60) + Rx
34: Visual inspection with acetic acid at age 40 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	VIA(40)*+HPVAC (12, $.60) + Rx

Intervention	Abbreviation
35: Smear test every five years for ages 20–65 + HPV vaccinations starting at age 12 at cost US$0.60	Pap(5,20,65)*+HPVAC (12, $.60)
36: Smear test every five years for ages 20–65 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	Pap(5,20,65)*+HPVAC (12, $.60) + Rx
37: Annual smear test for ages 20–30 then annual smear test with HPV vaccination for ages 30–65 + HPV vaccinations starting at age 12 at cost US$0.60	Pap (1,20,30) & Pap/ HPV(1,30,65)*+HPVAC (12,$.60)
38: Annual smear test for ages 20–30 then annual smear test with HPV vaccination for ages 30–65 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	Pap (1,20,30) & Pap/ HPV(1,30,65)*+HPVAC (12,$.60)+Rx
39: Triennial smear test for ages 20–30 then triennial smear test with HPV vaccination for ages 30–65 + HPV vaccinations starting at age 12 at cost US$0.60	Pap (3,20,30) & Pap/ HPV(3,30,65)*+HPVAC (12,$.60)
40: Triennial smear test for ages 20–30 then triennial smear test with HPV vaccination for ages 30–65 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	Pap (3,20,30) & Pap/ HPV(3,30,65)*+HPVAC (12,$.60)+Rx
41: Smear test every five years for ages 20–30 then smear test with HPV vaccination every five years for ages 30–65 + HPV vaccinations starting at age 12 at cost US$0.60	Pap (5,20,30) & Pap/ HPV(5,30,65)*+HPVAC (12,$.60)
42: Smear test every five years for ages 20–30 then smear test with HPV vaccination every five years for ages 30–65 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	Pap (5,20,30) & Pap/ HPV(5,30,65)*+HPVAC (12,$.60)+Rx
43: Smear test at ages 35, 40, and 45 + HPV vaccinations starting at age 12 at cost US$0.60	Pap (35,40,45)* +HP-VAC (12,$.60)
44: Smear test at ages 35, 40, and 45 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	Pap (35,40,45)* +HP-VAC (12,$.60)+Rx
45: HPV vaccination at ages 35, 40, and 45 + HPV vaccinations starting at age 12 at cost US$0.60	HPV (35,40,45)* +HP-VAC (12,$.60)
46: HPV vaccination at ages 35, 40, and 45 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	HPV (35,40,45)* +HP-VAC (12,$.60)+Rx
47: Visual inspection with acetic acid at ages 35, 40, and 45 + HPV vaccinations starting at age 12 at cost US$0.60	VIA (35,40,45)* +HP-VAC (12,$.60)
48: Visual inspection with acetic acid at ages 35, 40, and 45 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	VIA (35,40,45)* +HP-VAC (12,$.60)+Rx
49: Smear test at age 40 + HPV vaccinations starting at age 12 at cost US$0.60	Pap (40)* +HPVAC (12,$.60)
50: Smear test at age 40 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	Pap (40)* +HPVAC (12,$.60)+Rx
51: HPV vaccination at age 40 + HPV vaccinations starting at age 12 at cost US$0.60	HPV (40)* +HPVAC (12,$.60)
52: HPV vaccination at age 40 + HPV vaccinations starting at age 12 at cost US$0.60 + cancer treatment	HPV (40)* +HPVAC (12,$.60)+Rx

HPV= human papillomavirus.

Table 3. *Model inputs for cost effectiveness analysis of breast cancer control in WHO sub-Saharan African sub-region AfrE and South East Asian sub-region SearD*

Variable	Assumption	Data source
Distribution of prevalent cases (2005) and incident cases (2005–14) without breast cancer control programme:		Sankaranarayanan et al[10]*
Stage I	9.4%	
Stage II	14.2%	
Stage III	58.0%	
Stage IV	18.4%	
Distribution of incident cases (2005–14) in presence of optimal breast cancer programme:		Bland et al[11]†
Stage I	49.0%	
Stage II	37.4%	
Stage III	8.6%	
Stage IV	5.0%	
Case fatality rate of untreated patients (2005–14):		Sankaranarayanan et al[10]*
Stage I	0.020	
Stage II	0.063	
Stage III	0.150	
Stage IV	0.300	
Case fatality rate of treated patients (2005–14):		Bland et al[11]†
Stage I	0.006	
Stage II	0.042	
Stage III	0.093	
Stage IV	0.275	
Disability weight:		Murray and Lopez[12]; Norum et al[13]; Launois et al[14]; de Koning et al[15]‡
Stage I	0.068	
Stage II	0.070	
Stage III	0.072	
Stage IV treated	0.073	

**Combined data on breast cancer survival and disease staging from studies in Bombay, Bangalore, Barshi, Madras, Rizal, Chiang Mai, and Khon Kaen. These data, collected at International Agency for Research on Cancer (IARC), give the best available overview of survival and cancer stage distributions in Asian countries. Because of lack of similar data in sub-Saharan Africa, we assumed the IARC data to represent this region as well. These data represent the absence of breast cancer control strategies.*

†Data on breast cancer survival and disease staging based on a large sample size and specific per treatment. These data represent the presence of an optimal breast cancer control programme.

‡Health state valuation were based on the Burden of Disease study following standard WHO-CHOICE methods. Since only a single health state valuation is available for breast cancer, other studies were used to develop health state valuations for each cancer stage. The referred studies are the only studies that differentiate health state valuations for breast cancer by stage.

Table 4. *Model inputs for cost effectiveness analysis cervical cancer control in WHO sub-Saharan African sub-region AfrE and South East Asian sub-region SearD*

Variable	Assumption	Data source
Efficacy of HPV vaccination against HPV genotypes 16 and 18	100%	Kim et al[17]
Cervical smear test:		Goldie et al[21]
Sensitivity of detecting low grade lesions	0.60	
Specificity of detecting low grade lesions	0.95	
HPV DNA testing:		Goldie et al[21]
Sensitivity of detecting low grade lesions	0.84	
Specificity of detecting low grade lesions	0.88	
Visual inspection with acid (VIA):		Goldie et al[21]
Sensitivity of detecting low grade lesions	0.68	
Specificity of detecting low grade lesions	0.85	
Cervical smear + HPV DNA tests combined:		Kim et al[22]
Sensitivity of detecting low grade lesions	0.94	
Specificity of detecting low grade lesions	0.93	
Disability weight for cervical cancer	0.075	Murray and Lopez[12]

HPV= *human papillomavirus; Estimates of incidence and case fatality reductions derived from modelling the above data are listed in table A3.1 in appendix 3 on bmj.com.*

Table 5. *Model inputs for cost effectiveness analysis of colorectal cancer control in WHO sub-Saharan African sub-region AfrE and South East Asian sub-region SearD*

Variable	Assumption	Data source
Faecal occult blood test:		Wagner et al[23]*
Sensitivity for detecting polyps	0.1	
Specificity for detecting polyps	0.9	
Sensitivity for detecting cancer	0.6	
Specificity for detecting cancer	0.9	
Sigmoidoscopy:		Wagner et al[23]*
Sensitivity for detecting polyps and cancers	0.4	
Specificity for detecting polyps and cancers	0.9	
Colonoscopy:		Wagner et al[23]*
Sensitivity for detecting polyps and cancers	0.9	
Specificity for detecting polyps and cancers	1.0	
Digital rectal examination:		Herrinton et al[24]†
Sensitivity for detecting polyps and cancers	0.04	
Specificity for detecting polyps and cancers	1.0	
Eat more fruit and vegetables campaign:		
Increased consumption	12.4%	Dixon et al[25]‡
Decrease in cancer risk per 80 mg increase	0.01	Lock et al[26]§

Variable	Assumption	Data source
Disability weights for colorectal cancer:		Murray and Lopez[12¶]
Diagnosis and treatment	0.08	
Watchful waiting	0.08	
Metathesis	0.75	
Terminal	0.81	

Estimates of incidence and case fatality reductions were derived from modelling the above data and are listed in table A3.1 in appendix 3 on bmj.com.

**Consensus values from systematic literature reviews for the US Office of Technology Assessment.*

†Highest available level of evidence, from a single case-control study.

‡Largest available health promotion campaign, in state of Victoria, Australia.

§Meta-analysis of available literature.

¶Burden of Disease study following standard WHO-CHOICE methods.

For cervical cancer, screening interventions(plus removal of lesions as required) included Pap smears (Pap), HPV-DNA testing, visual inspection with acid (VIA) and combinations of Pap with HPV-DNA testing at various frequencies. Vaccination against the human papillomavirus (HPV) in a scenario where a booster dose is required every ten years [5, 16] assumed an efficacy of 100% against genotypes 16 and 18 [17], which together account for around two-thirds of cervical cancers in low-income countries [18-20]. Treatment of cervical cancer included chemotherapy, radiotherapy and surgery. Details on assumptions on intervention effectiveness are provided in Table 4, whereas the modeling design is provided in Appendix 2.

For colorectal cancer, a range of one-off (at age 50) and repeated (every 5 or 10 years) screening strategies were assessed, including faecal occult blood test (FOBT), sigmoidoscopy, colonoscopy and - despite uncertain evidence as to its efficacy - digital rectal examination (DRE) with subsequent removal of polyps and cancerous lesions as needed. The estimated impact of these strategies on the incidence of colorectal cancer ranged from 2.6% (i.e. one-off FOBT aged 50) to over 50% (e.g. colonoscopy every 10 years; annual FOBT plus sigmoidoscopy every 5 years) [6]. Treatment strategies included radiotherapy, chemotherapy and surgery. In addition, the preventive effect of a mass media campaign focused on higher fruit and vegetable consumption was considered. Details on assumptions on intervention effectiveness are provided in Table 5, whereas the modeling design is provided in Appendix 3.

At present, cancer control strategies in many Sub-Saharan African and Southeast Asian countries mainly rely on treatment of - often - advanced cases in referral hospitals, with treatment availability varying widely in and among countries in the regions under study. At present, there is low to very low coverage of cervical cancer vaccination or screening programs in the regions under study [27] – in South-Africa, coverage of screening by Pap smear is around 10%, while in India, this is less than 1% [28]. However, screening by VIA is likely to be more common. Screening programs for colorectal or breast cancer are virtually absent [29].

Intervention costs

WHO-CHOICE employs an ingredients approach to costing, such that resources used in the implementation of an intervention (e.g. outpatient visits or diagnostic tests) are specified in detail and the unit costs of these resources are determined separately. For example, for the breast cancer analysis, patient-level patterns of resource use (i.e. initial evaluation, local treatment and follow-up) were based on clinical practice guidelines [30, 31], and are summarized in Groot et al [4]. Since only a small proportion of all presenting women are diagnosed with breast cancer, most of the resources used for initial evaluation correspond to women diagnosed as not having breast cancer. Screening in the extensive cancer programme included mammographic screening of women aged 50–70 years, with further diagnostic tests on referral. Stage-specific treatment protocols for treating cervical cancer were based on standard practice in high-income countries [32, 33]. Resource quantities for the delivery of screening tests and treatment procedures for cervical and colorectal cancer (salaries, room use, drugs and disposable and reusable equipment) were retrieved from a South African database [34]. Over and above these facility-level resources, estimates of the resources needed to set up and maintain screening programmes were generated, based on a standardized procedure [35] and predicted numbers of human and other resources required to implement the programmes (e.g. 4-5 administrative posts per million population for notification, coordination, follow-up and monitoring activities [5, 6]. Details on resource use patterns are provided in Appendices 1-3.

Unit costs of non-traded goods - including salaries of health and administrative workers, as well as inpatient and outpatient services - were retrieved from the WHO-CHOICE database (http://www.who.int/choice/costs), which reports region-specific values derived from econometric estimation [36]. Drug prices were obtained from the International Drug Price Indicator Guide, marked up for international and local transportation costs [37,38]. Unit costs of laboratory, diagnostic and screening tests, as well as surgical procedures, derived on the basis of the aforementioned South African database, are provided in Appendices 1-3.

Unit costs were combined with resource-use patterns (described in more detail in Appendix 2b) to estimate costs per patient treated. Total patient costs in the population were then calculated as the cost per patient treated multiplied by the number of patients treated (calculated from the modelled annual incidence of disease multiplied by the coverage level and the proportion of cases diagnosed and treated in the covered population). All costs were reported in year 2005 international dollars (I$) to facilitate more meaningful comparisons across regions (I$1 buys the same quantity of health care resources in the Sub-Saharan African and Southeast Asian regions as it does in the United States. Cost estimates in Sub-Saharan Africa in I$ should be divided by a factor 2.3 to obtain US$ cost estimates for Kenya (in, Southeast Asia cost estimates should be divided by a factor 3.1 to obtain US$ cost estimates for India) [8]. All costs and effects are discounted at 3%, following standardized WHO-CHOICE analysis [9].

Cost-effectiveness

Dividing total implementation costs of each intervention by its effects generates a simple average cost-effectiveness ratio (ACER), relative to a comparator situation of no intervention. In addition to average CERs, incremental cost-effectiveness ratios (ICERs) are reported for the successive set of interventions that would be selected at expanding levels of resource availability, starting with the intervention with the lowest cost per DALY averted, then moving to the next most cost-effective combination intervention out of the remaining available set of interventions. An intervention that is more costly and/or less effective than other more efficient interventions is denoted as 'dominated'.

Uncertainty

Estimating the cost-effectiveness of interventions is inherently uncertain. To deal with this, we plot results on a double-logarithmic scale, so as to ascertain order-of-magnitude differences (e.g. I$ 10-100 versus I$ 100-1,000 per DALY averted). Second, we classify results according to defined cost-effectiveness thresholds: WHO-CHOICE calls an intervention yielding a healthy year of life for less than three times gross domestic product (GDP) per capita 'cost-effective', and an intervention yielding a healthy year of life for less than one times GDP per capita, 'very cost-effective'. In the sub-regions considered here, an intervention yielding a DALY for less than I$ 2,000 is considered highly cost-effective. Interventions yielding a DALY at a cost greater than three times GDP per capita (i.e. > I$ 6,000) are considered 'not cost-effective', while those with a cost-effectiveness ratio falling between I$ 2,000 and I$ 6,000 are considered 'cost-effective' in these sub-regions [39]. Finally, for the subset of interventions that are not dominated and therefore fall on the cost-effectiveness frontier, we undertook a probabilistic uncertainty analysis using the MCLeague software program [40]. We also assessed the impact of removing age-weights or discounting on baseline results via one-way sensitivity analysis for interventions with 95% coverage.

Results

Cost, effects and cost-effectiveness of interventions are listed in Table 6 (Sub-Saharan Africa) and Table 7 (Southeast Asia), and rank ordered on the basis of their ICER (the Tables do not include dominated interventions, i.e. those that are more costly and less effective than (combinations of) other interventions). The focus here is on determining the most efficient set of interventions, first within and then across the disease-specific groups (cost, effect and cost-effectiveness of all interventions are listed in appendix table 4, 5 and 6 for respectively cervical, colorectal and breast cancer control).

In both regions, certain interventions in cervical cancer control (i.e. screening through Pap smears or VIA in combination with treatment) and colorectal cancer control (i.e. increasing the coverage of treatment interventions) cost less than I$ 2,000 per DALY averted and can thus be considered highly cost-effective. In the African sub-region, screening for colorectal cancer (i.e. by colonoscopy at age 50 in combination with treatment) costs less than I$ 6,000 per DALY averted and can be considered cost-effective. In both regions, certain interventions in breast cancer control (treatment of all stages in combination with mammography screening) cost between I$ 2,000 and I$ 6,000 per DALY averted and can be considered cost-effective. Below we discuss the findings in detail.

In breast cancer control, treatment of all stages in combination with mammography screening costs between I$ 2,248-4,596 per DALY averted in both regions. At an optimal coverage level of 95%, this optimal program would avert 381 and 595 DALYs per one million population in Southeast Asia and Sub-Saharan Africa respectively, at a cost of between I$ 1.38 and I$ 1.68 per capita (i.e. around US$ 0.45-0.55). In both regions, treatment of stage I costs between I$ 3,800 and I$ 4,548 per DALY averted, whereas treatment of stage IV costs more than I$ 49,000 per DALY averted, and is the least cost-effective option (these interventions are less effective and/or more costly than other combination in breast cancer control, and therefore not reported in Tables 6 and 7).

For cervical cancer, screening 50% of the target population through a one-off Pap smear at age 40, with lesion removal and treatment as required, represents the single most cost-effective strategy in both Sub-Saharan Africa and Southeast Asia (I$ 307 and 142 per DALY averted, respectively). In both regions, the next most cost-effective cervical cancer intervention is treatment of invasive cancer with an appropriate combination of surgery, chemotherapy and radiotherapy. Also, in both regions, screening by means of VIA instead of Pap is slight more effective, but also more costly, and therefore less cost-effective. In Sub-Saharan African, adding a HPV vaccination program to the provision of Pap smears at age 40 and treatment as required can be considered very cost-effective if a cost per dose of US$ 0.60 cents can be realized. In the Southeast Asia, a HPV vaccination program is not cost-effective even at the same low vaccine price. Adding a booster vaccination every 10 years in addition to such strategies has a negligible impact on health outcomes but substantially increases costs and hence incremental cost-effectiveness values.

In colorectal cancer control, the most cost-effective strategy is the increased coverage of treatment interventions – at 95% coverage this would yield 792 and 868 DALYs per one million people in Southeast Asia and Sub-Saharan Africa respectively, at a cost of around I$ 0.30 per capita in both regions (i.e. around US$ 0.10). Once treatment has been scaled up, it would still be cost-effective to introduce colonoscopy screening at age 50 in the Sub-Saharan Africa. The incremental cost and cost-effectiveness of all other assessed interventions makes them much less attractive options.

Table 6. *Costs, effects, and cost effectiveness of interventions to combat breast, cervical, and colorectal cancer in WHO sub-Saharan African sub-region AfrE*

Intervention	Coverage (%)	Annual cost per capita ($Int)	Annual DALYs averted per million population	Cost effectiveness ratio		Rank*
				Average	Incremental	
Breast cancer						
BRE-6: Optimal programme (treatment of stages I–IV cancer, plus biannual mammographic screening)	50	0.68	313	2248	2248	8
BRE-12: Optimal programme	80	1.09	501	2253	2261	9
BRE-18: Optimal programme	95	1.34	595	2323	2696	10
Cervical cancer						
ALIGN TO MARGINCVC-129: Smear test at age 40 (with lesion removal) + cancer treatment	50	0.14	462	307	307	1
CVC-4: Treatment of invasive cancer (by surgery, chemotherapy, and/or radiotherapy)	95	0.24	606	401	702	4
CVC-51: Smear test at age 40 + HPV vaccinations starting at age 12 at cost of US$0.60 per vaccine dose + cancer treatment	95	0.41	829	497	756	5
CVC-35: VIA at age 40 + HPV vaccine from age 12 at US$0.60 per vaccine dose + cancer treatment	95	0.42	834	500	972	6
CVC-49: VIA at ages 35, 40, 45 + HPV vaccine from age 12 at US$0.60 per vaccine dose+ cancer treatment	95	0.48	872	550	1675	7
CVC-37: Smear test every five years for ages 20–65 + HPV vaccine from age 12 at US$0.60 per vaccine dose+ cancer treatment	95	0.72	934	772	3906	12
CVC-34: Smear test every three years for ages 20–65 + HPV vaccine from age 12 at US$0.60 per vaccine dose+ cancer treatment	95	0.92	950	970	12 425	14
CVC-43: Smear test every five years for ages 20–30 then smear test with HPV vaccination every five years for ages 30–65 + HPV vaccine from age 12 at US$0.60 per vaccine dose + cancer treatment	95	1.00	956	1048	13 705	15
CVC-33: Annual smear test for ages 20–65 + HPV vaccine from age 12 at US$0.60 per vaccine dose+ cancer treatment	95	1.41	971	1456	27 139	17
CVC-39: Annual smear test for ages 20–30 + then annual smear test with HPV vaccination every five years for ages 30–65 + HPV vaccine from age 12 at US$0.60 per vaccine dose+ cancer treatment	95	2.73	984	2773	100 075	18

Intervention	Coverage (%)	Annual cost per capita ($Int)	Annual DALYs averted per million population	Cost effectiveness ratio		Rank*
				Average	Incremental	
Colorectal cancer						
CRC-35: Cancer treatment (by surgery, chemotherapy, and/or radiotherapy)	80	0.27	792	336	336	2
CRC-10: Cancer treatment	95	0.35	1031	336	337	3
CRC-18: Colonoscopy at age 50 (with surgical removal of polyps) + cancer treatment	95	0.65	1115	585	3630	11
CRC-14: Colonoscopy screening every 10 years + cancer treatment	95	0.87	1138	766	9598	13
CRC-15: Annual faecal occult blood test + sigmoidoscopy every 5 years (with surgical removal of polyps) + cancer treatment	95	1.10	1153	952	15 548	16

HPV=human papillomavirus, VIA=visual inspection with acetic acid.

**Rank ordered on the basis of incremental cost effectiveness ratios.*

Table 7. *Costs, effects, and cost effectiveness of interventions to combat breast, cervical, and colorectal cancer in WHO South East Asian sub-region SearD*

Intervention	Coverage (%)	Annual cost per capita ($Int)	Annual DALYs averted per million population	Cost effectiveness ratio		Rank*
				Average	Incremental	
Breast cancer						
BRE-6: Optimal programme (treatment of stages I–IV cancer plus biannual mammographic screening)	50	0.87	201	4338	4338	8
BRE-12: Optimal programme	80	1.40	321	4362	4401	9
BRE-18: Optimal programme	95	1.68	381	4399	4596	10
Cervical cancer						
CVC-129: Smear test at age 40 (with lesion removal) + cancer treatment	50	0.19	1327	142	142	1
CVC-4: Treatment of invasive cancer by surgery, chemotherapy, and/or radiotherapy	95	0.27	1507	182	477	3
CVC-23: Smear test at age 40 + cancer treatment	95	0.46	1755	264	757	4
CVC-7: VIA at age 40 (with lesion removal) + cancer treatment	95	0.48	1765	269	1240	5
CVC-21: VIA at ages 35, 40, and 45 (with lesion removal) + cancer treatment	95	0.53	1796	294	1719	6

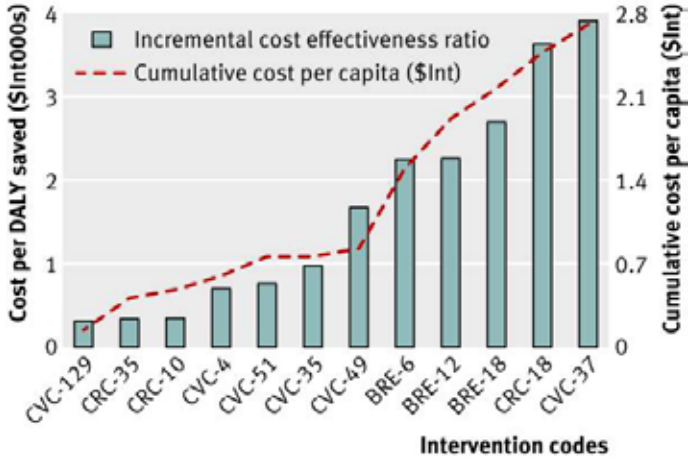
Intervention	Coverage (%)	Annual cost per capita ($Int)	Annual DALYs averted per million population	Cost effectiveness ratio		Rank*
				Average	Incremental	
CVC-17: Smear test at ages 35, 40, and 45 (with lesion removal) + cancer treatment	95	0.55	1803	303	2886	7
CVC-34: Triennial smear test for ages 20–65 + HPV vaccinations starting at age 12 at cost of US$0.60 per vaccine dose+ cancer treatment	95	0.85	1822	467	16 051	13
CVC-41: Triennial smear test for ages 20–30 then triennial smear test with HPV vaccination for ages 30–65+ HPV vaccinations starting at age 12 at cost of US$0.60 per vaccine dose + cancer treatment	95	1.41	1837	770	36 764	15
CVC-39: Annual smear test for ages 20–30 then annual smear test with HPV vaccination for ages 30–65+ HPV vaccinations starting at age 12 at cost of US$0.60 per vaccinedose + cancer treatment	95	2.77	1854	1493	81 629	17
Colorectal cancer						
CRC-10: Cancer treatment by surgery, chemotherapy, and/or radiotherapy	95	0.31	868	362	362	2
CRC-17: Sigmoidoscopy at age 50 (with removal of polyps) + cancer treatment	95	0.51	891	574	8291	11
CRC-18: Colonoscopy at age 50 (with removal of polyps) + cancer treatment	95	0.73	914	794	9318	12
CRC-14: Colonoscopy screening every 10 years + cancer treatment	95	1.04	926	1124	28 017	14
CRC-15: Annual faecal occult blood test + sigmoidoscopy every 5 years (with surgical removal of polyps) + cancer treatment	95	1.63	939	1735	42 940	16

VIA=visual inspection with acetic acid, HPV=human papillomavirus.

**Rank ordered on the basis of incremental cost effectiveness ratios.*

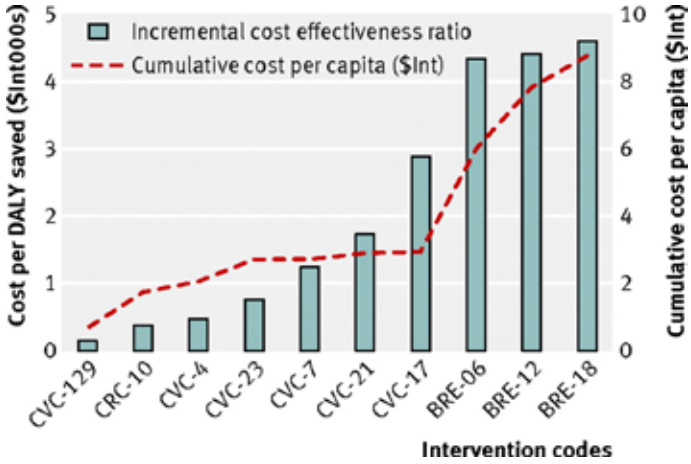
The incremental cost and cost-effectiveness of these interventions are illustrated in Figure 1 and Figure 2, which include only interventions considered cost-effective (i.e. with a cost per DALY below I$ 6,000). These graphs reveal the cost implications of adding in successively less cost-effective or more comprehensive interventions, showing for example the cumulative cost per capita associated with the provision of one of the more cost-effective interventions for each of the three cancers is less than I$ 1 in both regions.

Figure 1. *Incremental cost and cost effectiveness of interventions to combat breast, cervical, and colorectal cancer in WHO sub-Saharan African sub-region AfrE*



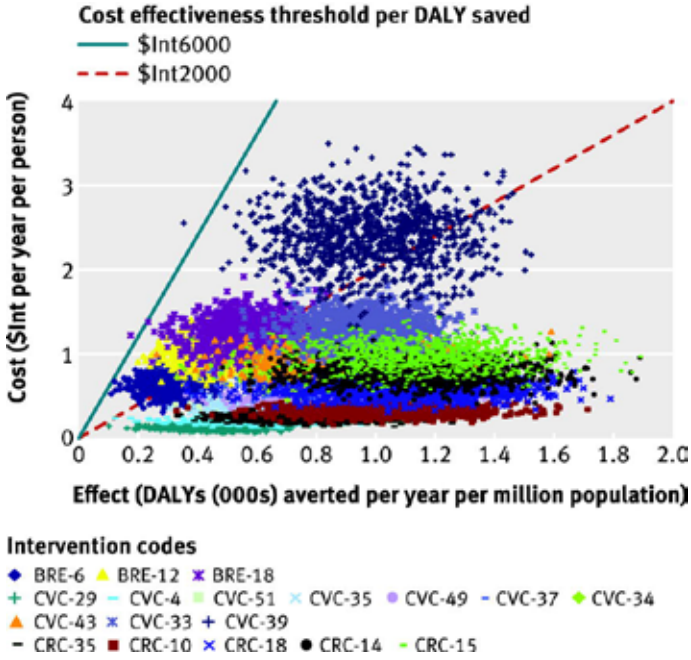
See table 6 for explanation of intervention codes.

Figure 2. *Incremental cost and cost effectiveness of interventions to combat breast, cervical, and colorectal cancer in WHO South East Asian sub-region SearD.*



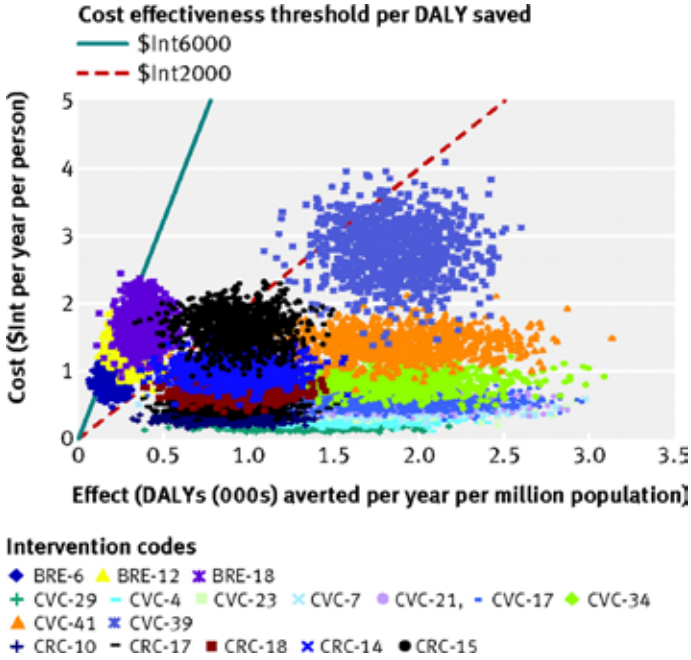
See table 7 for explanation of intervention codes.

Figure 3. *Probabilistic uncertainty analysis of interventions to breast, cervical and colorectal cancer in WHO sub-Saharan African sub-region Afr-E.*



See *table 6 for explanation of intervention codes.*

Figure 4. *Probabilistic uncertainty analysis of interventions to breast, cervical and colorectal cancer in WHO South East Asian sub-region Sear-D*



See *table 7 for explanation of intervention codes.*

The probabilistic uncertainty analysis depicted in Figures 3 and 4 shows the impact of plausible variations in total costs and total effects and shows that the average cost-effectiveness ratio of most interventions would retain a classification of 'highly cost-effective' and 'cost-effective', respectively, after taking into account such uncertainty. A similar logic would apply to the incremental cost-effectiveness ratios. One-way sensitivity analysis (Appendices 7-8) shows that for both sub-regions and all three diseases, removing age weights in the calculation of DALYs has a moderate impact on cost-effectiveness (CER rising slightly or falling by up to 20%). Removing discounting as well as age weighting had a far larger influence, increasing health outcomes and thereby lowering (i.e. improving) cost-effectiveness values markedly (by 45%-90%).

In addition, we performed sensitivity analysis on the price of HPV vaccines: the approximate threshold price for HPV vaccine to become very cost-effective is US$ 6 in Sub-Saharan Africa and US$9 in Southeast Asia. If booster doses are required every 10 years, a cost as low as US$ 1.30 in Sub-Saharan Africa and US$ 0.90 in Southeast Asia is required to render the intervention cost-effective (not in Table).

Discussion

Principal findings

Our analyses suggest that a number of highly cost-effective interventions to combat cervical and colorectal cancer are available in Sub-Saharan Africa and Southeast Asia. In cervical cancer, these include screening through Pap smear or visual inspection with acetic acid, in combination with treatment. In colorectal cancer, increasing treatment coverage is highly cost-effective (screening through colonoscopy is cost-effective in the African sub-region). In breast cancer control, mammography screening in combination with treatment of all stages is cost-effective.

Policy implications

In breast cancer control, our analyses have shown that treating early stage breast cancer is more cost-effective than treating late-stage disease. Results indicate that priorities in national breast cancer control programs would be the implementation of an extensive cancer control program (including active mammography screening and treatment of all stages). Although such a program reflects the economic attractiveness of diagnosing breast cancer at an earlier stage, many developing countries may not be able to meet its total costs (including the required infrastructure, logistics, and expertise). Given the limited available resources, priorities are probably best directed at treatment of early stage disease and at developing a less expensive means of early diagnosis. We did not evaluate clinical breast examination or breast self-examination because currently there is no consensus on their value alone or in addition to mammography. Nevertheless, together with other ways of raising awareness, clinical breast examination and breast self-examination could be a cost-effective means by which to diagnose breast cancer earlier in resource-poor settings.

In cervical cancer control, an increased coverage of treatment services and low-cost screening programs like Pap smears or VIA are both economically very attractive in both regions. Increasing treatment coverage is a challenging task, and requires ample investments in hospital infrastructures (especially in rural areas) along with the training of staff in surgery, chemotherapy and radiotherapy. Also the implementation of screening through Pap smears is complex, and requires the routine availability of laboratory facilities. In that respect, the implementation of screening by means of VIA, which does not require laboratory facilities, may be relatively less complex. In Sub-Saharan Africa, an HPV vaccination program could also be considered if vaccine prices are very low. However, analyses on HPV vaccines involve a greater level of uncertainty [41,42] – for example, there is no observational evidence on the duration of efficacy (conservatively assumed to be 10 years in our analysis) and the price is unknown. We assumed a vaccine price as low as US$ 0.60 based on a figure twice that of the current yellow fever vaccine cost and the precedent of falling hepatitis B vaccine costs in the 1990s. At the current price (over US$100 per dose in developed countries), the vaccine is unlikely to be cost effective in developed, let alone in developing, countries; in the latter, it will also be highly unaffordable. An additional question is the acceptability of a vaccination to prevent cervical cancer initially aimed at twelve-year old girls, especially in religious cultures [43]. However, it should be noted that the reported cost-effectiveness ratios for HPV vaccination are upwardly biased in the sense that our model did not take into account the burden of condyloma [44] or recurrent respiratory papillomatosis [45] on health systems, nor the potential cost savings or DALY reductions when a quadravalent vaccine is used [46,47]. Targeting screening and vaccinations at HIV positive persons could be a way of improving cost-effectiveness, since HIV infection is associated with elevated cervical cancer levels [48]. A more sensitive but less specific HPV test (carelHPV) will soon be available in developing countries at a far lower cost than the Hybrid Capture II test [49] - this is likely to improve the relative cost-effectiveness of HPV-DNA testing against other PAP, VIA (and vaccine-based) interventions and in turn improve the relative effectiveness of PAP and HPV-DNA combinations against other interventions.

In colorectal cancer control, increasing the low level of treatment coverage is the most cost-effective intervention in both the regions considered here. Screening by colonoscopy at age 50 in combination with treatment is also cost-effective in the Sub-Saharan Africa. The use of DRE is not cost-effective despite its low cost as only a very small percentage of polyps can be detected. However the cost-effectiveness ratio of DRE is overestimated as the model did not include the potential effects of reducing mortality from prostate cancer. We also evaluated the introduction of a fruit and vegetable campaign, and the provision of price subsidies to fruit and vegetables, but these are only able to avert a very modest level of disease burden and are accordingly not cost effective in relation to their effect on colorectal cancer alone. However fruit and vegetable campaigns could be cost-effective when possible protective effects on other diseases are taken into account.

Comparison with other studies

Several studies have reported on the global and regional cost-effectiveness of interventions targeting breast, cervical and colorectal cancer [4-6]. However, studies have been carried out in isolation, which prevents the cost-effectiveness of the different interventions in cancer control being directly compared. In addition, these studies have been analyzed using year 2000 demographics and price levels. This study directly compares cost and effects of interventions targeting breast, cervical and colorectal cancer, using more recent price levels. This allows the identification of most efficient strategies to improve cancer control in the regions considered. For example, our analyses show that certain interventions in cervical cancer and colorectal cancer control are more cost-effective than others in breast cancer control, in both regions considered.

Strengths and limitations

Over and above the limitations of these cancer-specific models, a number of more general shortcomings need to be mentioned. Firstly, our analysis considers costs and effectiveness of interventions, but does not address health systems constraints making implementation of the interventions difficult. For cancer control strategies constraints may be in terms of infrastructure, logistics, and expertise, and these factors should be taken into account when making actual programme decisions. For example, the expansion of colonoscopy services in colorectal cancer control or mammography screening in breast cancer control will be constrained by lack of trained health personnel. Likewise, the successful implementation of Pap and HPV-DNA interventions will depend on laboratory capacity. Also, issues of acceptability may play a role – e.g. of the HPV vaccine [50]. We therefore stress that cost-effectiveness analysis should only be considered as one input in the decision-making process, and should not be used in a formulaic way. Second, for some interventions, assumptions on effectiveness were based on studies in other (high-income) settings (many under trial conditions) in the absence of local evidence. This may overestimate the effectiveness that can be achieved in the regions of analysis, and therefore the economic attractiveness of interventions. However, our uncertainty analysis indicates that study results are robust to alternative assumptions. Third, and closely related, patterns of resource utilization were sometimes based on clinical practice guidelines in western settings, e.g. in the cost analysis of breast cancer treatment. The relevance of these guidelines was then carefully assessed and adjusted where necessary (see Groot et al. [4] for more detail). Fourth, we did not evaluate all possible interventions in cancer control, and our selection of interventions for analysis was pragmatic and somewhat arbitrary. Policy makers should be aware of this, and should not limit their choice of interventions to those included in this analysis. Fifth, the analyses did not include economies of scale resulting from the joint provision of breast, cervical or colorectal cancer interventions. In reality, cost saving may be realized when breast and cervical cancer screening activities are jointly organized. Sixth, in the absence of reliable data, the analyses did not include costs of patients seeking or undergoing care, not did it include changes in productivity as a result of the interventions [51-53]. Seventh, the analysis evaluates interventions at 50%, 80% and 95% geographic coverage levels, following standardized WHO-CHOICE methodology.

The higher coverage levels may not be achievable in the short term but are included to indicate the long-term efficiency resulting from economies of scale as more people are reached [54]. Eight, analyses are carried out at the regional level but important differences in costs and/or effectiveness of interventions may exist between countries in the same region. Since decision making is made at the country (as opposed to regional) level, more refined estimates of costs, effects and cost-effectiveness should be made at the county-level, based on country specific data. A good example is the contextualization of WHO-CHOICE regional results to the country-level in Mexico, as reported in this series [55]. The above limitations should be considered in the overall aim of WHO-CHOICE analysis to provide broad indications, i.e. a crude bird's eye view, on the cost-effectiveness of a range of interventions to inform general policy discussions rather than to deliver precise estimates on a specific intervention [7-9].

Acknowledgements

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1. What is already known on this topic
- Several studies have reported on the global and regional cost-effectiveness of interventions targeting breast, cervical and colorectal cancer.
- However, studies have been carried out in isolation, which prevents the cost-effectiveness of the different interventions in cancer control being directly compared.
- In addition, these studies have been analyzed using year 2000 demographics and price levels

2. What this study adds
- This study directly compares cost and effects of interventions targeting breast, cervical and colorectal cancer, using more recent price levels.
- Analyses show that a number of highly cost-effective interventions to combat cervical and colorectal cancer are available in Sub-Saharan Africa and Southeast Asia. In cervical cancer control, these include screening through Pap smear or VIA, in combination with treatment. In colorectal cancer, increasing treatment coverage is highly cost-effective (screening through colonoscopy is cost-effective in the African sub-region). In breast cancer control, mammography screening in combination with treatment of all stages is cost-effective.

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CHAPTER

Multi-criteria decision analysis of breast cancer control in low- and middle-income countries

development of a rating tool for policy makers

The fewer the facts, the stronger the opinion

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Abstract

Background

The objective of this study was to develop a rating tool for policy makers to prioritize breast cancer interventions in low- and middle- income countries (LMICs), based on a simple multi-criteria decision analysis (MCDA) approach. The definition and identification of criteria play a key role in MCDA, and our rating tool could be used as part of a broader priority setting exercise in a local setting. This tool may contribute to a more transparent priority-setting process and fairer decision-making in future breast cancer policy development.

Methods

First, an expert panel (n=5) discussed key considerations for tool development. A literature review followed to inventory all relevant criteria and construct an initial set of criteria. A Delphi study was then performed and questionnaires used to discuss a final list of criteria with clear definitions and potential scoring scales. For this Delphi study, multiple breast cancer policy and priority-setting experts from different LMICs were selected and invited by the World Health Organization. Fifteen international experts participated in all three Delphi rounds to assess and evaluate each criterion.

Results

This study resulted in a preliminary rating tool for assessing breast cancer interventions in LMICs. The tool consists of 10 carefully crafted criteria (effectiveness, quality of the evidence, magnitude of individual health impact, acceptability, cost-effectiveness, technical complexity, affordability, safety, geographical coverage, and accessibility), with clear definitions and potential scoring scales.

Conclusions

This study describes the development of a rating tool to assess breast cancer interventions in LMICs. Our tool can offer supporting knowledge for the use or development of rating tools as part of a broader (MCDA based) priority setting exercise in local settings. Further steps for improving the tool are proposed and should lead to its useful adoption in LMICs.

Keywords

Multi-criteria decision analysis, priority setting, breast cancer

Introduction

As the second most common cancer in the world and the most common cancer in women, breast cancer is an important health problem globally [1]. Although it was originally considered to be a disease of the developed world, low- and middle-income countries (LMICs) are experiencing large increases in incidence [2]. Mortality-to-incidence rates remain relatively high in these areas [3], possibly due to relatively poor breast cancer control strategies (e.g. awareness raising, early detection, treatment) and differences in cultural beliefs [2-4]. Because strong early detection programs are beneficial, the World Health Organization (WHO) seeks to improve appropriate breast cancer control programs in LMICs.

Cost-effectiveness analyses (CEAs), based on the maximization of health benefits, have often been used for the selection of breast cancer control strategies. To provide an evidence base for the cost-effectiveness of breast cancer interventions in LMICs, a consortium of the WHO, Erasmus University Rotterdam, the Radboud University Nijmegen Medical Center, and the Susan G. Komen for the Cure foundation initiated an international study in 2010 [5]. Such CEAs may help governments decide how to spend scarce health care resources more efficiently. However, decision-makers often deviate from CEA results because other principles such as equal treatment and priority to the worst-off [6-8] and other factors like feasibility or acceptability influence decisions, as well [9-11]. Ignorance about these criteria may induce implementation problems or inequality among certain patient groups [12-14].

Multi Criteria Decision Analysis (MCDA) is a well-accepted framework that can simultaneously assess multiple criteria for priority setting of interventions [15]. Different approaches of MCDA are proposed but contain at least the following elements: 1) selection of relevant interventions, 2) selection of criteria for priority setting, 3) collecting evidence and rating the performance of interventions on selected criteria, 4) deliberation on the evidence and performance of interventions with the aim to select the best interventions for implementation [16-19].

Several studies have shown the potential of MCDA in prioritizing health interventions, however, it has not yet been applied for the selection of breast cancer control interventions [20-23]. Recently, MCDA has been criticized for being technocratic and conceptually challenging for local decision makers [21]. Therefore, the development of a tool to support local policy makers in selecting criteria and in rating the performance of interventions on these criteria is warranted.

The objective of this study is to develop a rating tool to assess breast cancer interventions along the continuum of care, within the context of the overarching breast cancer CEA project [5]. The rating tool will be composed of criteria, criteria definitions, criteria weights and rating scales to measure the overall impact of breast cancer interventions and support the priority setting process. Such a rating tool can be used in a broader, MCDA based, priority setting process to develop cancer control strategies in a local setting.

Methods

To develop the rating tool we established an expert panel (n=5) of breast cancer and priority-setting experts from WHO and the Radboud University Nijmegen Medical Centre. The expert panel consisted of two health economists, a scientific researcher, a public health specialist and a student on health technology assessment. Three of the experts are co-authors of this article (KV, SZ and JL). A detailed overview of the considerations made by the expert panel in the development of the rating tool is provided as additional information (additional file 1). Below we describe the most important steps that were taken to develop the tool.

A literature search using PubMed and Google Scholar was performed for the identification of a first set of predefined criteria. Different combinations of the terms 'criteria', 'values', 'factors', 'priority setting', 'decision making', and 'policy making' were used as the query. The expert panel discussed the list in order to avoid overlap among the criteria. For the remaining criteria, clear definitions were defined with the help of glossaries and documents published by the WHO [25-27].

To develop the scoring scales, another literature study was performed for each criterion of this predefined list. When no or little information was available, scoring scales were mainly based on discussions with the expert panel.

The Delphi study

The list of predefined criteria and scoring scales was further refined by the opinion of experts from all over the world. A Delphi study was chosen because of the anonymity of participants, the opportunity to include participants globally, and the time and money available to conduct the study [28]. Delphi studies have proven to be appropriate for finding a core list of evaluation criteria [29].

Participants

Experts were selected following WHO selection criteria that include a balanced geographical and gender representation, expertise in the technical area (particularly in LMICs), and absence of any relevant interest in the personal declaration of interest form. Twenty-nine experts with expertise in priority setting or breast cancer policies in LMICs were involved, ensuring methodological as well as substantive quality. Experts were identified by approaching authors of relevant articles and by snowball sampling. Among the experts there were epidemiologists, cancer survivors, pathologists, guideline-developers, public health specialists, radiotherapists, surgeons, researchers, managers, strategists and ethicists.

First round

In this round, the list with criteria based on the performed literature study was presented to the participants. The participants were asked to score the criteria on five-point Likert scales, according to whether they agreed that interventions scoring high on the criterion should be more prioritized (1= strongly disagree, 2= disagree, 3= neutral, 4= agree, 5= strongly agree). The experts could give comments on the list and mention whether important criteria were missing. In addition, the definitions and scoring scales of the criteria were presented and participants were asked to provide comments. Likert scales were chosen for this first round because this method is reviewed as acceptable for a Delphi study and is simple and easy to perform [30].

Figure 1. *Overview of the development of the criteria list.*

Stage	Results	Number of criteria
Literature study	'Effectiveness', 'Time until effect emerges', 'Quality of evidence', 'Efficiency', 'Acceptability', 'Appropriateness', 'Accessibility', 'Competence', 'Continuity', 'Safety', 'Affordability', 'Impact on health budget', 'Human resources', 'Sustained access to materials and drugs', 'Magnitude of individual benefit', 'Type of medical service', 'Severity of disease-status', 'Capacity to benefit', 'Lifetime equality of health', 'Age of target group', 'Life threatening disease-status', 'Rare disease-status'/ 'need of orphan drugs', 'Responsibility for health status', 'SES (wealth, income and education) of target group', 'Area of residence', 'Race'/ 'Ethnicity and religion of target group', 'Catastrophic levels of health expenditure', 'Productivity losses', 'Positive and negative externalities', 'Political willingness', 'Funding sources'/ 'Donors', 'Media attention', 'International priorities'	33 criteria
Expert panel	'Effectiveness' ('Size of the effectiveness', 'Certainty of the evidence' and 'Time until the effect emerges'), 'Cost-effectiveness', 'Feasibility' ('Reach', 'Technical complexity', 'Capital intensity' and 'Cultural acceptability'), 'Safety', 'Accessibility', 'Severity of breast cancer', 'Age', 'Magnitude of individual health impact', 'Catastrophic health expenditures'	9 criteria, one with 3 and one with 4 subcomponents
Delphi first round	- 'Severity of breast cancer' and 'Age' removed - 'Time until the effect emerges' removed - 'Size of the effectiveness' and 'Certainty of the evidence' separated as individual criteria - 'Cultural acceptability' combined with 'Safety' and 'Reach' combined with 'Accessibility' - 'Technical complexity' and 'Capital intensity' separated as individual criteria - 'Political will' included as a new criteria - 'The certainty of the evidence' renamed into 'The strength of the evidence', 'Accessibility' renamed into 'Equal access', 'Capital intensity' renamed into 'Affordability', 'Cultural acceptability' renamed into 'Acceptability'	10 criteria
Delphi second round	- 'Political will' removed - 'Equal access' divided into two different criteria: 'Accessibility' and 'Geographical coverage' - 'Safety' divided into two different criteria: 'Safety' and 'Acceptability' - 'Catastrophic health expenditures' combined with 'Accessibility' - 'The strength of the evidence' renamed into 'The quality of the evidence'	10 criteria
Final list	'Effectiveness', 'Quality of evidence', 'Magnitude of individual health impact', 'Acceptability', 'Cost-effectiveness', 'Technical complexity', 'Affordability', 'Safety', 'Geographical coverage', 'Accessibility'	10 criteria

Table 1. *Initial criteria including Likert scores and important comments given in the Delphi study*

	Average Likert scores	Median Likert scores	Range of Likert scores	Most important comments
Effectiveness	4.75	5	4-5	-Effectiveness is covered by its components. Effectiveness should therefore be removed and its components should be independent criteria, otherwise they will overlap.
- Size of effectiveness	4.70	5	3-5	-No important comments.
- Certainty of the evidence	4.35	5	1-5	-Not related to effectiveness only. The strength of the evidence varies by criterion for any given intervention. Much simpler and effective to include considerations of certainty of evidence in assigning scores for all given criterion.
- Time until the effect emerges	3.09	3	1-5	-Time preference for immediate effects goes against principles of intergenerational equity, and is especially inappropriate for preventive services. Therefore this criterion should be removed.
Cost-effectiveness	4.25	4.5	1-5	-MCDA might replace C/E. We can have costs but "effectiveness" is defined by the sum of the criteria so adding this criterion introduces double-counting. -Efficiency cannot be replaced by costs since higher costs do not per se mean lower efficiency as the effectiveness may be higher.
Feasibility	4.23	4	2-5	-This should be four different criteria, otherwise they will overlap each other. -See comments accessibility.
- Reach	4.46	5	2-5	-No important comments.
- Technical complexity	3.5	3.5	1-5	-This criterion should not be limited to capital costs but also explicitly include operating costs required from the health system.
- Capital intensity	3.75	4	1-5	-No important comments.
- Cultural acceptability	4.13	4.5	1-5	
Safety	4	4	2-5	-The importance of safety may vary with respect to whose safety (provider vs. patient) and what is at stake, while the level of acceptability may remain the same. Therefore acceptability and safety should be kept separated.
Accessibility	4.33	4.5	1-5	-Accessibility due to geographical coverage of an intervention ('Reach') is not the same as accessibility due to socio-economic status. Therefore this criterion should be about equal access for patients with different socio-economic status, while geographical coverage should be covered by another criterion ('Reach').
Severity of breast cancer	3.26	3	1-5	-Of course I think that palliative care is very important. On the other hand, if you do nothing for all the people with earlier stage cancer, the cancer will progress and they will all need palliative care. So you could treat people with stage 1 or 2 cancer and most of them will not experience late stage cancer, therefore will not need palliative care. I guess I don't find this a useful way to think about breast cancer.
Age	3.29	3.5	1-5	-Ages of patients with breast cancer don't seem appropriate even if one wanted to create prioritized age groups, which I wouldn't.
Magnitude of individual health impact	3.83	4	1-5	-No important comments.
Catastrophic health expenditures	4.17	5	1-5	-Affordability is about whether the health system can afford an intervention and catastrophic health expenditures is about whether patients can afford it. Extreme health expenditures might however be covered by accessibility, because patients with lower socio-economic status cannot afford high health expenditures.

Second round

This second round showed the scores and comments given in the first round, together with the adaptations to which they had led. Subsequently, participants were asked whether they agreed on the adaptations and if they could clarify their answers.

Third round

Based on the proportion of participants agreeing on the adaptations made after the first round and on the comments provided, some final changes were made to the criteria list. These final criteria and their definitions and scoring scales were shown to the participants, who were asked whether they agreed that this final list contained the most relevant criteria for the prioritization of breast cancer interventions. Furthermore, participants were asked to divide 100 points over the criteria according to their relative importance for the evaluation of breast cancer interventions.

The analysis

The analysis of the answers was both quantitative and qualitative. After the first Delphi round, mean and median scores on the Likert scales for "the importance" of criteria were calculated. The second round resulted in a percentage of participants who agreed with the suggested adaptations. After the third round, the mean and median weights given according to the importance of criteria were calculated. All participant comments were quantitatively analyzed.

Results

The literature search on criteria resulted in a total of 33 criteria (Figure 1). After the expert panel discussed these criteria, nine criteria remained for the Delphi study. Two criteria, effectiveness and feasibility, were divided into three and four subcomponents. For each of these nine criteria and the subcomponents, a definition and a potential scoring scale were defined.

Participants

Out of 72 experts who were asked, 29 were willing to participate. Of these, 17 were experts on priority setting, and 12 were experts on breast cancer policies. The first questionnaire was completed by 23 participants, the second questionnaire by 19 participants, and the third questionnaire by 15 participants. Reasons for not completing a questionnaire were private circumstances and disagreement with the aim of this research (n=1). Most participants, however, gave no reason.

First round

Based on the results of the first round, two criteria ('Severity of breast cancer' and 'Age') and one of the components ('The time until the effect emerges') were suggested for removal; two of the components were suggested to be combined with two criteria; and all the other components were suggested for separation into different criteria. Also, a new criterion was suggested ('Political will'), two definitions were refined, and four scoring scales were adapted. These adaptations led to a list of 10 criteria. For all criteria, except for the criterion 'Effectiveness', there was divergence in Likert scale scores. The average and median Likert scale values and most important comments on the criteria are shown in Table 1.

Second round

Based on the results of the second round, the new suggested criterion ('Political will') was removed again because participants argued that political will would also depend on the results of interventions on the other criteria; political will changes too often; and MCDA aims at a more fair priority-setting process while political will might even be clearly unfair. Two criteria ('Equal access' and 'Acceptability') were separated into two different criteria ('Geographical coverage' and 'Accessibility'; 'Acceptability' and 'Safety'); two criteria were combined ('Catastrophic health expenditures' and 'Acceptability'); and some small refinements to most of the definitions and scoring scales were made. An overview of the changes made in the criteria list is shown in Figure 1. The second round resulted in a final list of 10 criteria (Table 4).

Third round

All participants agreed that the list after the second round covered the most relevant criteria for the prioritization of breast cancer interventions. Three participants mentioned, however, that some criteria might be still overlapping. As one participant noted: "Doing the relative weighting exercise above, I realized that some criteria are overlapping and it was difficult to assess independent relative weights to them; for example, 'effectiveness' and 'quality of the evidence' are inseparable whereas we would not perhaps say something is effective if the quality of the evidence is weak." There were also doubts about 'cost-effectiveness' being covered by the 'affordability' and 'effectiveness' and about 'safety' being covered by 'effectiveness' and 'geographical coverage' being covered by 'effectiveness'. The criterion 'geographical coverage' was rated relatively low in its importance for the evaluation of breast cancer interventions, followed by 'safety' and 'affordability', respectively. The importance of the criterion 'Effectiveness' was rated highest (Table 2).

Table 2. *Final criteria list for the prioritization of breast cancer interventions including weights*

	Definition	Potential scoring scales	Average weight* (min-max)	Median weight
Effectiveness [31-35]	Effectiveness is the extent to which an intervention impacts the most relevant health-related outcomes (e.g. time to recurrence or healthy life years gained). In comparison of effectiveness of interventions, it is important to note that the most relevant health-related outcome should be consistent for all interventions under consideration [25].	Size of the effect (e.g. in a population of 1 million people): 0 less effective (e.g. < 50 healthy life years gained a year) 1 effective (e.g. ≥ 50 < 100 healthy life years gained a year) 2 very effective (e.g. ≥ 100 healthy life years gained a year) [30]	17.33 (5 - 50)	15
Quality of the evidence [31, 32, 35, 37, 38]	The risk of bias and the extent of the confidence that the evidence is adequate to support a particular decision or recommendation [39].	0 very little or limited confidence in the evidence: the estimated values may be substantially different from the outcomes in reality 1 moderately confident about the evidence: The estimated values are likely to be close to the outcomes in reality, but there is a possibility that it is different 2 very confident that the estimated values lie close to the outcomes in reality [33]	11.93 (0 - 20)	12
Magnitude of individual health impact [32, 38]	Interventions offering small benefits for many may be viewed differently from those offering large benefits for a few. When one of the two is preferred above the other, interventions providing the preferred effect (concentrated or dispersed) might be more prioritized [32].	0 the intervention is not accepted by some people and it is not likely that this can be changed 1 the intervention is not accepted by some people but it is likely that this can be changed with some extra effort (e.g. special education) 2 the intervention is accepted by almost all people	8.67 (5 - 15)	10

	Definition	Potential scoring scales	Average weight* (min-max)	Median weight
Acceptability [26, 35, 35, 38]	The extent to which the intervention is judged as suitable, satisfying or attractive by different stakeholder groups (e.g. patients, providers or politicians). The acceptability depends on people their norms, beliefs and values [26, 40].	0 poor affordability (e.g. costs > 1 US$ per capita) 1 moderate affordability (e.g. costs > 0.50 ≤ 1 US$ per capita) 2 good affordability (e.g. costs ≤ 0.50 US$ per capita) [20]	8.47 (0 - 20)	15
Cost-effectiveness [31, 32, 35, 37, 40]	The capacity to produce the maximum output for a given monetary input [25].	0 there is a risk of severe adverse effects (life threatening) to patients or a risk of adverse effects (of any kind) to providers 1 there is a risk of mild adverse effects to patients 2 there is no risk or a risk of very mild adverse effects (adverse effects which will completely recover within a month) to patients	7.87 (0 - 15)	10
Technical complexity [26, 34]	Other types of inputs required in addition to monetary inputs to implement and to keep providing the intervention. (These include human resource requirements, both quantitative and qualitative, and organizational requirements. The potential to integrate the intervention into an already existing health system should also be taken into account [26].	0 the intervention does not cover (most) people who live far away from cities. 1 the intervention does not cover some people who live far away from cities. 2 the intervention covers (almost) all people	5.47 (0 – 13)	10
Affordability [26, 31, 34, 35, 38]	The monetary input (e.g. capital investments and operational costs) required from the health system to implement and to keep providing the intervention [26].	0 poor affordability (e.g. costs > 1 US$ per capita) 1 moderate affordability (e.g. costs > 0.50 ≤ 1 US$ per capita) 2 good affordability (e.g. costs ≤ 0.50 US$ per capita) [20]	8.47 (0 - 20)	10
Safety [31, 34]	Safety is the practical certainty that adverse effects to patients or providers will not result from exposure to an intervention under defined circumstances [27].	0 there is a risk of severe adverse effects (life threatening) to patients or a risk of adverse effects (of any kind) to providers 1 there is a risk of mild adverse effects to patients 2 there is no risk or a risk of very mild adverse effects (adverse effects which will completely recover within a month) to patients	7.87 (0 - 15)	5
Geographical coverage [26, 32, 34, 35]	The ability of the intervention to be reached by the target population, independent of their living place [26].	0 the intervention does not cover (most) people who live far away from cities. 1 the intervention does not cover some people who live far away from cities. 2 the intervention covers (almost) all people	5.47 (0 – 13)	13
Accessibility [31, 37]	Patients with a different socioeconomic status or a different income should be able to make equal use of the intervention [32].	0 the intervention is not accessible to many patients 1 the intervention is not accessible to some patients 2 the intervention is accessible to (almost) all patients	10.6 (0 – 20)	

NOTE: References were used to identify the criteria in first instance. The Delphi study may have resulted in adaptations in definitions or scoring scales than originally found in the literature

** weights were calculated by asking participants to divide 100 points over the criteria according to their relative importance for the evaluation of breast cancer interventions.*

** weights were calculated by asking participants to divide 100 points over the criteria according to their relative importance for the evaluation of breast cancer interventions.*

Discussion

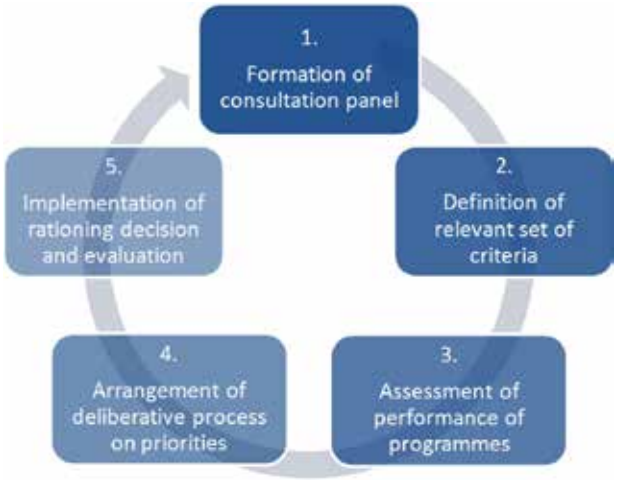
This study describes the development of a rating tool to measure the impact of breast cancer interventions based on multiple criteria in LMICs. Ten criteria, including definitions and potential scoring scales, have been indicated. The results of this study show that effectiveness, quality of the evidence, magnitude of individual health impact, acceptability, cost-effectiveness, technical complexity, affordability, safety, geographical coverage, and accessibility seem to be important principles in the selection of breast cancer control strategies. Although selecting and defining interventions and criteria for breast cancer control is context specific, we think that this rating tool can be a starting point for local policy makers as part of a broader, MCDA based, priority setting process.

Use of the tool in a LMIC

The tool could be used as part of the integrated MCDA and accountability for reasonableness (A4R) approach for priority setting, recently proposed by Baltussen et al. [16] (Figure 2). This new approach combines strong components of both frameworks and requires a set-up of a multi-stakeholder consultation panel (step one). In this way a democratic learning process is started in which stakeholders are involved in all steps of the priority setting. Compared to the stand-alone MCDA framework, this combined approach may increase the acceptance of decisions among stakeholders and the likelihood of implementation of prioritized programs. The rating tool can be part of step two and three (Figure 1) of the approach that aim to identify criteria for priority setting and assess (i.e. rate) the performance of interventions on the selected criteria.

An important next step in the local use of the rating tool is to investigate how the tool and its components are understood in LMICs in a pilot study. Users of the tool could for example select relevant stakeholders (e.g. patients, lay-people policy makers, caregivers, public health specialists) and establish a consultation panel (step 1). These stakeholders could discuss the interventions, criteria, the attitude of decision-makers against the criteria and scoring scales using democratic elements (e.g. Nominal Group Technique) (step 2). After the collection of all relevant (local) evidence, the users could use our tool as an input for a performance matrix (step 3), and then interpret and deliberate on the results of this matrix (step 4 and 5). Users should be well informed and plan enough time for this process, and should try to ensure that the tool is perceived as a simple and legitimate way to frame policy discussions in a more rapid and balanced manner. The potential of this tool could also be investigated for other cancers.

Figure 2. *Elements of a priority setting process based on MCDA* [16]



Limitations of the study

Our study has a number of limitations. First, prior to the Delphi study, the expert panel made a selection of 9 criteria out of 33 criteria. This selection was based on overlap between criteria and whether criteria would be appropriate for the selection of breast cancer interventions. However, there is no certainty that personal preferences did not lead to bias in this selection.

Second, we used Delphi studies to define a list with core criteria including definitions and scoring scales. The Delphi method ensures participant anonymity and provides enough time to properly consider one's own answers and those of others. However, the Delphi questionnaire may not allow for adequate elaboration on difficult concepts such as equity and social welfare. Also, Delphi questionnaires can be relatively time consuming, which may have partly caused 14 participants to withdraw from this study. We do not expect that these withdrawals biased the results because they varied in gender and type of expert and the number of comments remained high in each questionnaire.

Third, the wide variety of comments and views of the participants made us aware of the difficulties in developing a clear, consensus-based, non-overlapping criteria list and scoring scales. There are many possible compositions and definitions of criteria [31-33]. Besides there are many ways to divide a scoring scale into different categories and this also depends on the variability of the interventions that are considered (i.e. discriminative power of the scoring scale). Further research should focus on more informed contextualized categories for scoring scales.

The difficulty of avoiding overlap between criteria may be explained by a lack of a broader theory on the relationship between criteria. Some disagreement between participants remained until the end of the process, and some overlap was still suspected in the final criteria list. These potential overlaps will need attention in the further development of this tool because criteria should preferentially be independent from each other [15, 42]. Especially effectiveness has a risk of overlap with other criteria, like cost-effectiveness, safety and geographical coverage. Further overlap between criteria should be identified and distinctions should be made and clearly described in the definitions.

Limitations of the tool

The tool also has some practical limitations that one should be aware of. First, the tool does not provide guidance to convert the performance matrix into a final prioritization of interventions. This tool stops at rating interventions after which a choice should be made based on a democratic learning process (figure 1). This tool does not facilitate a democratic learning process, which makes it less likely that good rated interventions are implemented. The accountability for reasonableness framework (A4R) is successful in introducing such a learning process [43]. We recommend making the tool part of the integrated MCDA A4R approach for priority setting in health as proposed by Baltussen et al. [16], however local capacity should be present or established to facilitate such a complete process.

Second, the proposed rating tool is based on decision-maker values and preferences while the views of other stakeholder groups are also considered important in priority setting exercises. Different stakeholder groups are likely to have different preferences for criteria [22, 44]. This limitation of the tool could be solved while applying the tool in a local setting. At that stage, other stakeholder groups (like patients, the public, and health care workers) can be asked to comment on the relevance of the criteria included in the tool and the relative importance and the tool can be adapted accordingly.

Third, there are limitations to the collection of information, and it may sometimes be difficult to assess interventions on certain criteria. This is however a problem across the field of health priority setting and we recommend to be transparent on the available evidence and its quality. A sensitivity analysis may help to give insight in the uncertainty of the scoring performances of intervention options. In this way, quality of evidence is not used as a single criterion but as an uncertainty factor per criterion per intervention [45].

Conclusion

This study describes the development of a rating tool to assess the impact of breast cancer interventions on multiple criteria. This tool may be a starting point for local decision makers that would like to conduct multi criteria decision analysis to set priorities for breast cancer control.

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Competing interests
The author(s) declare that they have no competing interests. The views expressed in this paper are those of the authors, and the funding organization has had no influence on them.

Authors' contributions
KV and SZ made substantial contributions to the conception and design of the study, acquisition of data, and analysis and interpretation of data. They also participated in the expert panel and drafted the manuscript. JL contributed to the design and methodology of the study and participated in the expert panel. NT assisted in the design of the study and has been involved in revising the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

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CHAPTER
10

General discussion

Progress lies not in extension, but in the knowledge of limitations

Thesis rationale

The general objective of this thesis is to improve the knowledge base on the cost-effectiveness of interventions for breast cancer control in LMICs. Evidence-based information on interventions that provide the greatest value for money can support LMICs in improving their national breast cancer control programs. To meet this objective, the research question addressed in this thesis is: What is the cost-effectiveness of a range of breast cancer control interventions along the continuum of care in a number of LMICs?

To answer this research question, this thesis first provides a systematic review of available cost-effectiveness estimates for breast cancer control in LMICs (Chapter two). It then demonstrates a method to predict the stage distribution of different breast cancer screening options, which can be used to estimate the effectiveness of screening interventions (Chapter three).

Next, a number of case studies are discussed that provide the costs, effects, and cost-effectiveness of breast cancer control interventions in five LMICs (Chapters four to seven). These case studies only include the individual perspectives of countries, and a more global perspective is also taken in this thesis (Chapter eight).

To comprehensibly guide LMICs in improving breast cancer control, this thesis also focuses on other considerations next to cost-effectiveness. The last study presented in this thesis therefore includes a generic rating tool that can be used in a broader priority-setting process (Chapter nine). This tool considers multiple other criteria, including cost-effectiveness, to support comprehensive breast cancer control strategies in LMICs.

The next section summarizes and further elaborates on the available cost-effectiveness evidence of five countries - Ghana, Mexico, Costa Rica, India, and Peru - to which this thesis contributes. Then, the global evidence used in this thesis will be considered using the results from Chapter eight and supplementary analyses. In the subsequent sections, the policy implications (exemplified by a case study from Colombia), limitations, and suggestions for future research that follow from this thesis will be discussed.

Interventions that provide the greatest health for money

Contributions of this thesis on individual countries

Our systematic review (Chapter two) shows that not many health economic studies on breast cancer control have been conducted in LMICs. A search of the international literature in January 2013 yielded 24 economic studies that evaluated different kinds of screening, diagnostic, and therapeutic interventions in various age and risk groups in LMICs [1]. However, out of these 24 studies, only seven presented functional cost-effectiveness results - these are studies from which cost-effectiveness ratios could be determined. In addition to the functional cost-effectiveness studies from our systematic review, cost-effectiveness estimates from five individual countries (Costa Rica, Ghana, India, Mexico, and Peru) are presented in this thesis (Chapters four to seven).

Table 1 provides an overview of the most cost-effective interventions based on the studies presented in this thesis. The interventions can be considered cost-effective if their incremental cost-effectiveness ratio (ICER) is less than three times the GDP per capita, which is a generic decision rule recommended by the World Health Organization.

Table 1. *Overview of the reported cost-effectiveness estimates of breast cancer control interventions in individual LMICs in this thesis.*

Country	Base year	GDP in per capita in base year	Number of interventi-ons analyzed	Model used	Control component of recommended intervention	Cost-effective-ness estimates (ICER min-max)	Most cost-effective intervention based on ICER
				Results from systematic review in this thesis			
Brazil [5]	2005	$4,739	2	Markov model	Treatment (Hormonal therapy)	$11,193 per LYS	Anastrozole, in relation to tamoxifen ($11,193/LYS)
China [6]	2012	$6,093	2	Markov model	Treatment (Radiotherapy)	$328 - 577 per QALY	Radiotherapy, in relation to no radiotherapy after breast conserving therapy ($233/LYS) and ($421/QALY)
China [7]	2008	$3,414	2	Markov model	Treatment (Chemotherapy)	$4,892 per QALY	TC, in relation to AC ($5,383/LYS) and ($4,892/QALY)
India [8]	2001	$466	11	MISCAN-model	Early detection (Population based screening)	$793 - $19257 per LYS	Single CBE screen at age 50 ($793/LYS)
Mexico [9]	2005	$7,824	101	WHO-CHOICE model	Early detection (Population based screening)	$1,625 - $21,983 per DALY	Treatment of all stages plus mammography screening ($21,983/DALY)
Morocco [10]	-	$2,861	2	-	Treatment (trastuzumab)	$663,000 per LYS	Treatment with trastuzumab for HER2 over expressing patients ($663,000/LYS)**
Vietnam [11]	-	$1,232	2	-	Treatment (Surgery)	$351 per LYS	Adjuvant oophorectomy and tamoxifen for hormone receptor positive operable breast cancer, compared to standard treatment ($351/LYS)

Country	Base year	GDP in per capita in base year	Number of interventi-ons analyzed	Model used	Control component of recommended intervention	Cost-effective-ness estimates (ICER min-max)	Most cost-effective intervention based on ICER
Results from original work in this thesis							
Costa Rica [1]	2009	$6,629	19	WHO-CHOICE model	Early detection (Population based screening)	$4,739 - $30,352 per DALY	Biennial CBE screening ($5,964/DALY)
Ghana [2]	2009	$649	17	WHO-CHOICE model	Early detection (Population based screening) Early detection (Breast health awareness)	$1,299 - $553,616 per DALY	Biennial CBE screening ($1,299/DALY) or mass media awareness raising (MAR) ($1,364/DALY)
Maharashtra, India [3]	2013	$3,650	21	WHO-CHOICE model	Treatment (Chemotherapy)	$1,406 - $58,664 per DALY	AC regimen combined with tamoxifen ($1,840/DALY) or CAF regimen combined with tamoxifen ($5,102/DALY)
Mexico [1]	2009	$8,416	19	WHO-CHOICE model	Early detection (Breast health awareness) Early detection (Population based screening)	$5,021 - $13,994 per DALY	Mass media awareness raising (MAR) ($5,021/DALY) or biennial mammography screening (age 50-70) ($12,718/DALY)
Peru [4]	2012	$4,068	94	WHO-CHOICE model	Early detection (Population based screening)	$4,125 - $87,243 per DALY	Triennial screening by CBE in rural areas (age 40-69) + triennial screening by CBE (age 40-49) and fixed mammography (age 50-69) in urban areas ($4,349/DALY)*

**Next to the ICER, affordability and complexity were considered as criteria.*

*** Cannot be considered cost-effective based on the WHO-CHOICE decision rule on cost-effectiveness analysis.*

***QALY** = Quality Adjuste Life Year; **LYS** = Life Year Saved; **DALY** = Disability Adjusted Life Year; **ICER** = Incremental cost effectiveness ratio, ratio of additional cost per additional life-year saved when next intervention is added to a mix on the intervention path (additional US$ per additional DALY saved). **CBE** = Clinical breast examination; **AC** = cyclophosphamide and doxorubicin ; **CAF** = cyclophosphamide ,doxorubicin and 5-fluoracil; **TC** = docetaxel, cyclophosphamide.; **HER2** = human epidermal growth factor receptor.*

Many of the breast cancer interventions in Table 1 relate to early detection or treatment strategies, and the cost-effectiveness estimates of these interventions vary greatly per country (ranging from $233 to $633,000 per life-year saved). Concerning early detection strategies for breast cancer control, the cost-effectiveness estimates for population-based screening are $793 per life-year saved (CBE screening, India), $1,299 (CBE screening, Ghana), $4,125 (mixed screening, Peru), $4,739 (CBE screening, Costa Rica), $5,021 (MAR, Mexico), and $21,983 per DALY averted (mammography screening, Mexico). The cost-effectiveness estimates for treatment interventions for breast cancer are $233 (radiotherapy, China) and $4,892 per QALY (chemotherapy, China) and $351 (oophorectomy, Vietnam), $1,406 (chemotherapy, India), $11,193 (hormonal therapy, Brazil), and $633,000 per life-year saved (trastuzumab, Morocco). Treatment with trastuzumab in Morocco cannot be considerd cost-effective according to the proposed threshold.

Some of the variation in these cost-effectiveness estimates can be explained by the many differing factors in these countries, including disease epidemiology, population structure, wages of healthcare personnel, inflation rates, drug costs, practice variation, utilization rates of equipment, and health financing system. However, it seems that most of the variation can be explained by differences in study characteristics and study objectives. Prior studies recommending treatment interventions did not include any early detection or palliative care interventions and used different comparator scenarios from studies recommending screening interventions. For example, the Brazilian study included only two hormonal treatment interventions, one of which served as a comparator scenario, whereas the Peruvian study included 94 interventions along the continuum of care for which "do nothing" served as the comparator scenario. Even the six WHO-CHOICE studies shown in Table 1 have differing study characteristics, mostly relating to the interventions analyzed. For example, the Indian study did not analyze early detection or palliative care interventions at all. The first Mexican study (base year 2005) did not analyze CBE screening or palliative care interventions. The second Mexican study (base year 2009) did not analyze opportunistic screening, mixed forms of screening (fixed vs. mobile), or upfront FNA.

Therefore, if recommendations are to be made for individual countries purely on the basis of cost-effectiveness, a closer look at the results for each study by control component is necessary. These components, which were described in the introduction section of this thesis, consist of early detection (breast health awareness, population based screening, opportunistic screening), diagnosis (clinical, pathological, lab/radiological), treatment (surgery, radiotherapy, chemotherapy, hormonal, and other therapy), follow-up and rehabilitation, and palliative care (Table 2).

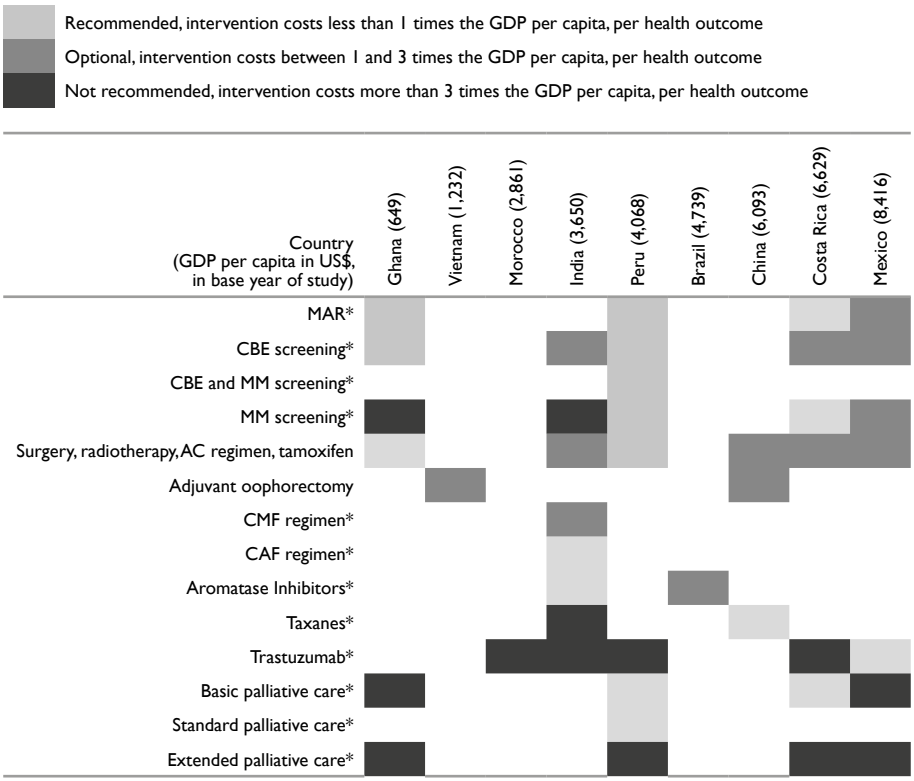
Cost-effectiveness estimates for the early detection component of breast cancer control indicate that CBE screening (ages 40–69) may be recommended for most countries. Mass media awareness-raising (MAR) could also play an important role in most countries, especially in countries with relatively poor stage breast cancer distributions and relatively inexpensive media costs. Mammography screening (ages 50–69), on the other hand, may only be recommended for countries with a relatively high GDP per capita (over $4,000) and relatively low mammography procedure costs. Mixed screening programs, such as CBE screening in rural areas and fixed mammography screening in urban areas, were only analyzed for Peru but could be important for all countries with a relatively high GDP per capita and relatively high urbanization rates.

Cost-effectiveness estimates for the treatment component of breast cancer control show that adjuvant radiotherapy and surgery are highly cost-effective. Treatment schedules that include standard radiotherapy, surgery, chemotherapy (AC regimen), and tamoxifen are also cost-effective. However, the results show that treatment of stages I to IV breast cancer only is less cost-effective than when treatment is combined with early detection strategies. More advanced treatment regimens that include CAF or aromatase inhibitors may only be recommended for countries with a relatively high GDP per capita (over $4,000), whereas treatment regimens that include taxanes may only be recommended for countries with a GDP per capita over $6,000. Trastuzumab therapy may only be recommended for countries with a GDP per capita above $8,000 dollars and seems not to be appropriate for most LMICs.

Remarkably, no cost-effectiveness research has been performed on interventions relating to diagnosis or to follow-up and rehabilitative breast cancer control components. This is remarkable, particularly for follow-up, since the cost of follow-up can account for 35% of the total healthcare costs per breast cancer patient.

The few estimates for the palliative care component of breast cancer control generally indicate that palliative care interventions are not cost-effective for most countries. More efficient palliative care strategies are those that comprise less expensive elements, such as oral morphines and home-based visits by volunteers. These strategies seem to be still relatively cost-effective in Peru and Costa Rica and could be important in LMICs were patients arrive mostly in advanced breast cancer stages.

Table 2. *Overview of recommended breast cancer interventions by control component based on cost-effectiveness estimates only*



MAR = Mass media awareness raising of breast cancer signs and symptoms; CBE = Clinical breast examination; MM = mammography; AC = cyclophosphamide and doxorubicin ; CMF = cyclophosphamide, methotrexate, fluorouracil; CAF = cyclophosphamide ,doxorubicin and fluoracil; Basic palliative care = only morphines and home based care by volunteers; Standard palliative care = only morphines and treatment of bone metastasis; Extended palliative care = morphines, treatment of metastases, home based care by professionals.

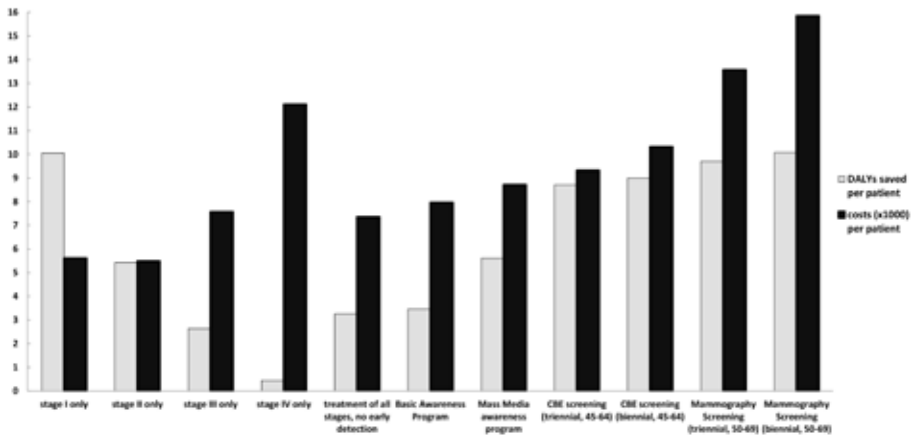
**Includes treatment of all stages (sugery, radiotherapy, AC regimen, tamoxifen).*

Global contributions of this thesis

Our results on the cost-effectiveness of breast cancer control in the African sub-region E (Afr-E) and Southeast Asian sub-region D (Sear-D) (Chapter eight) demonstrated that interventions combining mammography screening and treatment of all breast cancer stages can have a cost-effectiveness ratio equal to or less than the GDP per capita and are thus cost effective. The estimated cost-effectiveness ratios were 2,696 (Afr-E) and 4,596 (Sear-D) per DALY for mammography screening in the 50–69 age group with treatment of all stages.

The analysis in Chapter eight includes only two high-mortality world sub-regions; however, the analysis does not include estimates of CBE screening or breast health awareness raising strategies and we furthermore have estimates for the other 12 world sub-regions. These estimates can be used as a starting point for making choices on the wide spectrum of breast cancer control in countries for which country-specific estimates are currently unavailable. Pooling the results of all these sub-regions gives the rough average global costs and rough average global effectiveness estimates per patient (Figure 1).

Figure 1. *Global costs (US$) and effects (DALYs) per patient for breast cancer (2005 estimates)*



From this figure, rough global cost-effectiveness estimates can also be derived. Costs for treatment of stage I, II, III, and IV breast cancer are about $558, $1,011, $2,864, and $26,850 per DALY, respectively; globally, late-stage breast cancer management (stages III and IV) is twice as expensive as early-stage breast cancer management (stages I and II). Treatment of all stages comes at a global cost of roughly $2,260 per DALY averted. For early detection strategies, the rough breast health awareness costs are $2,297 (BAR) and $1,555 (MAR) per DALY. Population-based screening costs are $1,146 (biennial CBE), $1,071 (triennial CBE), $1,398 (triennial mammography), and $1,574 (biennial mammography) per DALY averted.

Figure 1 shows that early detection strategies can improve the cost-effectiveness of healthcare spending globally. However, early detection strategies may require additional investments that are higher than the resources required for only the treatment of breast cancer (treatment of all stages, no early detection). From a healthcare perspective, investments in early detection strategies are not cost saving. Using 2005 estimates, these additional investments range between $0.11 per capita (mass media awareness in Afr-E) and $5.26 per capita (biennial mammography screening in Western Pacific sub-region A).

Although additional investments for implementing early detection strategies can be substantial and may double breast cancer control expenditures, the health benefits to society that would accrue from these strategies - if implemented well and followed by appropriate treatment - would generally outweigh the additional costs. The average cost per unit of health spent will decrease because of early detection, allowing resources to be allocated more efficiently. Globally, in the absence of early detection strategies and when only treatment was available, about three DALYs would be averted per breast cancer patient. When early detection strategies would be implemented in combination with treatment the number of DALYs averted could increase threefold, to about 10 per breast cancer patient (Figure 1).

Implications for policymakers: Interventions that provide the greatest value for money

In LMICs, many breast cancer patients typically present with locally advanced or metastatic tumors. Shifting the stage distribution of the disease downward seems to be a necessary step toward improving health outcomes for these patients. The previous section argued that early detection strategies may increase the health of breast cancer populations threefold and that the cost per unit of health accrued by these strategies was lower than that of treatment only. Early detection strategies linked to appropriate treatment can therefore be considered relatively more cost-effective than treatment only, and investments in early detection most likely ensure that resources are allocated more efficiently.

From the perspective of cost-effectiveness, policymakers from LMICs should include early detection strategies in their national breast cancer control programs. Available diagnosis, treatment, and follow-up interventions are warranted, as these components are essential for the effectiveness of the entire breast cancer control program. In addition, screening interventions should always include an awareness-raising component to ensure an informed target population, proper breast health education for the general population, and adequate attendance rates. In general, all of these control components should be in place, and the lack of any component or referral system between these components could decrease the efficiency of the entire control program.

Whether to choose MAR, CBE screening, mammography screening, or mixed screening for early detection in a specific LMIC or whether to provide aromatase inhibitors, taxanes, or trastuzumab seems to depend on the many country-specific inputs that affect the cost-effectiveness of these interventions. The previous section showed that CBE screening strategies (ages 40–69) seem cost-effective in most LMICs and mammography screening (ages 50–69) is only cost-effective in those countries with sufficient resources (GDP per capita over $4,000). Early detection linked to essential treatment (surgery, radiotherapy, AC chemotherapy, tamoxifen) seems cost-effective in all LMICs, and could be complemented by aromatase inhibitors.

Providing taxanes or trastuzumab is generally not economically attractive unless LMICs have a GDP per capita over $6,000 or $8,000, respectively. Nevertheless, although the research presented in this thesis indicates that early detection strategies are cost-effective in a selection of LMICs, the current knowledge base for the costs and effects of breast cancer control strategies in many other LMICs is still inadequate. It is currently uncertain how early detection strategies will perform and how much they will cost if implemented in a specific LMIC. For example, important indicators such as attendance rates and sensitivity rates are often unavailable, but are essential in estimating the performance of screening programs (Chapter three). Hence, policy recommendations for specific LMICs based on the current cost-effectiveness evidence should be developed carefully and should account for some degree of uncertainty.

Decision makers often base their choices on the cost-effectiveness of interventions, for which this thesis provides evidence. In addition to this efficiency consideration, a policy maker will need to carefully consider the financial burden of interventions, especially in resource-poor settings. Which breast cancer control strategies to provide in a particular LMIC seems to depend predominantly on the amount of resources available in a particular country. The previous sections showed that the economical attractiveness of breast cancer control interventions relates to the GDP per capita. These sections also showed that additional investments are required to implement early detection strategies linked to appropriate treatment, which may double current spending on breast cancer control. In particular, screening strategies may be considered too expensive in LMICs; thus, in the decision-making process, the budget impact of breast cancer control strategies should always be considered.

Furthermore, in addition to affordability considerations, other factors can be of significant importance in considering certain breast cancer control strategies. One of the most fundamental problems for policymakers in LMICs is the lack of good surveillance and monitoring systems to provide accurate data on the burden of breast cancer and its risk factors. Another problem is the lack of various system-level factors, such as a lack of trained personnel and cancer services to support early detection services. In addition, communicable diseases tend to be prevalent in LMICs, and it can be difficult for policymakers to divert resources from communicable diseases to non-communicable diseases. Moreover, early detection strategies may be unethical in countries in which treatment is unaffordable or inaccessible or is only accessible to a small affluent part of the population [12].

In Chapter nine of this thesis, we explored the range of considerations for selecting breast cancer control strategies with international experts [13]. Ten criteria, including definitions and potential scoring scales, were selected: effectiveness, quality of the evidence, magnitude of individual health impact, acceptability, cost-effectiveness, technical complexity, affordability, safety, geographical coverage, and accessibility. The most important outcome of this study for policymakers is a rating tool to measure the impact of breast cancer interventions based on all these criteria simultaneously. This type of approach, which is called multi-criteria decision analysis (MCDA), is known for its potentially broader application in setting priorities in healthcare [14,15].

Hence, what LMICs should provide in their breast cancer control programs should not only be based on the interventions that provide the greatest health for money but also the interventions that provide the greatest value for money. This means maximizing the utility of breast cancer control programs using a broader trade-off process that includes all valuable criteria. Although selecting and defining interventions and criteria for breast cancer control based on MCDA should be context-specific, our proposed rating tool can be a starting point for local policy makers in LMICs as part of a broader priority-setting process.

Using more criteria than just cost-effectiveness; example for policymakers

To demonstrate the use of our developed rating tool, a short implementation experiment was performed in Colombia. The approach used and the results from this experiment are discussed in Box 1 and could be useful to policymakers from other LMICs.

Box 1. *MCDA in practice: The case of Colombia*

In this experiment, we estimated the value for money of fifteen breast cancer control interventions. The experiment was conducted in Colombia during a three-day cost-effectiveness policy workshop with a number of important Colombian policymakers, health professionals, and researchers. In the steps below we explain how the experiment was conducted.

Step 1: Fifteen breast cancer interventions were selected during a three-day cost-effectiveness workshop in Bogota (25 participants). Participants selected interventions form a predefined list that included early detection strategies as discussed in this thesis. Other interventions were added at the recommendation of a clinical expert group with experience on evidence-based guidelines for breast cancer. Next, relevant criteria were selected from a predefined list of 10 criteria as defined by our rating tool [13]. The 25 participants selected eight criteria through an individual ranking exercise in which participants could distribute 100 points over 10 criteria. Two criteria (required budget and confidence in evidence) were excluded because the participants found these criteria stringent and wanted to use them in a later stage of the experiment.

Step 2: Using the Nominal Group Technique (25 participants), the definitions of the eight criteria and their scoring scales were improved. Each participant was provided with a sheet of paper with the preliminary definitions of the eight criteria and their scoring scales. Participants were asked to write down everything that came to mind when considering these definitions and to provide improved definitions. Then, all alternative definitions were recorded on a flip chart and discussed after all alternatives were listed. Participants were invited to provide verbal explanation or further details for any of the definitions their colleagues produced. This was eventually followed by an anonymous voting process in which each participant could vote for the best definition.

Step 3: To obtain the weights of each criterion, a discreet choice experiment was performed with 18 participants using software from 1000 Minds [16,17]. Each participant was asked to answer a range of questions through the online environment, from which weights (utilities) for each criterion were automatically derived. The final criteria, definitions, scoring scales, and their weights are presented in Appendix Table A1; these could be used by other LMICs.

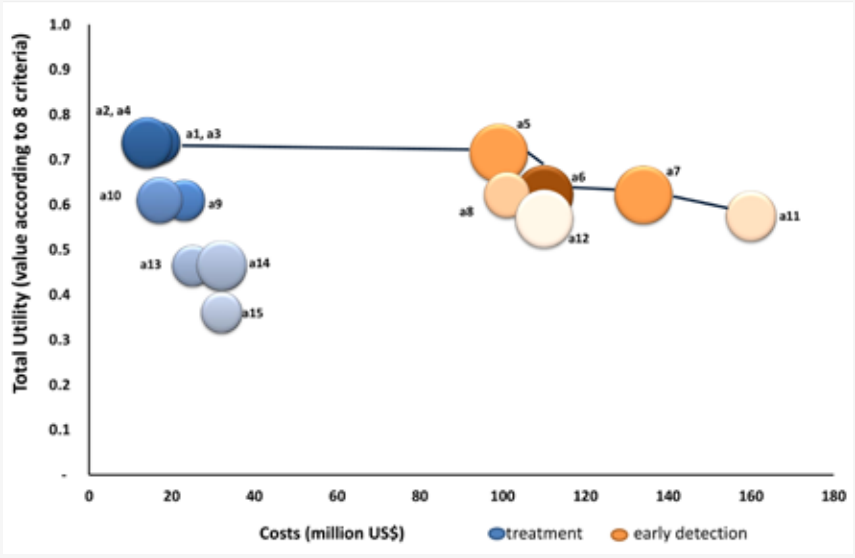
Step 4: Evidence was collected to analyze the extent of performance of the 15 interventions on each of the eight selected criteria. Most of the evidence was derived from reviewing the international literature; where possible, Colombian scientific literature was used. The evidence for all 15 interventions was analyzed by criterion by two researchers and summarized using a performance matrix. This performance matrix was completed through the online 1000 Minds environment to identify the interventions with the most value relative to other interventions[17].

A visual representation of the results of the Colombian performance matrix (Figure 3) shows the total value (utility) of each intervention according to its performance on all eight criteria simultaneously (y-axis). These values are plotted along the required budget of each intervention (x-axis). The size of each bubble represents the level of uncertainty of each intervention's total value; hence, interventions with overlapping bubbles could have similar values, making it unclear as to which intervention is preferable.

Figure 3 shows that treatment interventions a1 to a4 (aromatase inhibitors or switch therapy in stages I and II) have the greatest value for money. Since the bubbles of these interventions overlap, it is difficult to distinguish the values of these interventions, and all of them could be recommended. The figure also shows that with regard to early detection interventions, biennial CBE screening in women aged 40–49 provides the greatest value for money (a5). Intervention a6 (triennial CBE screening in women aged 40–49 + mammography screening in women aged 50–69) is the second-best option.

Hence, when more criteria than just cost-effectiveness are considered simultaneously in Colombia, this experiment indicates that CBE screening strategies (ages 40–69) should receive even greater priority in LMICs and that aromatase inhibitors could be provided in addition to essential treatment. Providing mammography screening, taxanes, and trastuzumab should be given less priority in LMICs. The total value for money was based on eight relevant criteria: cost-effectiveness, number of potential beneficiaries, safety, acceptability, effectiveness, geographical coverage, severity of the health condition, and technical complexity. This proposed MCDA approach could therefore be more realistic, integrated, and useful in practice for decision making on breast cancer control.

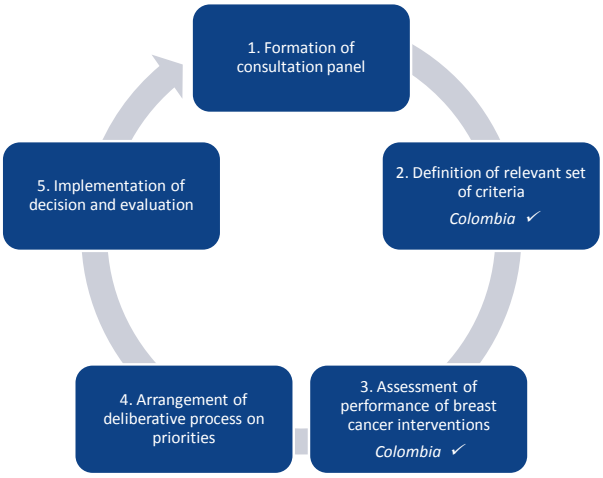
Figure 2. Values (utilities) of 15 breast cancer interventions based on the proposed MCDA approach in Colombia.



a1:Treatment + aromatase inhibitors for hormonal positive women in stage I a2: Treatment + aromatase inhibitors for hormonal positive women in stage II a3: Treatment + switch therapy for hormonal positive women in stage I a4: Treamtent + switch therapy for hormonal positive women in stage II a5: Biennial CBE screening in women aged 40-69 + treatment of all stages a6: Triennial CBE screening in women aged 40-69 + mammography screening in women aged 50-69 + treatment of all stages a7: Biennial CBE screening in women aged 40-49 + mammography screening in women aged 50-69 + treatment of all stages a8: Biennial mammography screening in women aged 50-69 + treatment of all stages a9: Treamtent + trastuzumab for HER2 positive breast cancer in stage I a10: Treatment + trastuzumab for HER2 positive breast cancer in stage IIa a11: Biennial mammography screening in women aged 40-69 + treatment of all stages a12: Opportunistic mammography screening in women aged 50-69 + treatment of all stages a13: Treatment + trastuzumab for HER2 positive breast cancer in stage IV a14: Treament + Lapatinib + Trastuzumab for HER2 positive breast cancer in stage IV a15: Treatment + Lapatinib for HER2 positive breast cancer in stage IV

The arguments and the proposed approach in this section indicate that cost-effectiveness analyses based on the maximization of health benefits may help governments select breast cancer control strategies. However, policymakers often deviate from CEA results because other principles and (ignorance of) these principles may lead to sub-optimal priorities. The results from Chapter nine showed that cost-effectiveness is as important as the effectiveness criterion. The results from our Colombian experiment show that cost-effectiveness is less important than two other criteria, number of potential beneficiaries and safety (Appendix Table A1). This confirms that more criteria should be considered than just cost-effectiveness in deciding which breast cancer control interventions should be given the highest priority. The approach proposed above and the tools presented in this thesis should be used as one part of a broader priority setting approach in a local setting (Figure 4, steps 2 and 3). This broader approach requires the setup of a multi-stakeholder consultation panel and a democratic learning process in which local stakeholders are involved in all the priority-setting steps [13,18]. This broader approach fosters broad acceptance of the prioritized intervention among all stakeholders and the actual implementation of the intervention.

Figure 3. Broader MCDA apporoach for priotiry setting of breast cancer control interventions [18]



Limitations of this thesis and future research

The studies presented in this thesis have a number of limitations, and future research should try to address these. First and most important, evidence from high-quality experimental studies on the costs and effectiveness of early detection strategies is currently lacking in most LMICs [1,12]. At present, only one randomized controlled trial has investigated an early detection strategy for breast cancer control in a LMIC [19]. Observational studies are available but are difficult to interpret. To arrive at the cost-effectiveness estimates in this thesis, we used a model approach that only has a theoretical proof of concept, and the extrapolation of our model to other settings (external validity) is not yet proven (Chapter three). The economic evidence provided in this thesis is therefore subject to many assumptions, and this may have biased our estimates. There seems to be a general lack of evidence on (less established) early detection interventions such as awareness-raising and screening by tactile imaging, ultrasound, breath tests, or CBE screening. However, there is also a lack of studies on shorter follow-up and diagnostic work-up management schemes as well as preventive and palliative interventions. It is necessary to evaluate these types of interventions, particularly in LMICs, as they have the potential to be economically attractive [12,20–22].

Second, national cancer registries in the LMICs for which cost-effectiveness estimates are provided in this thesis were often unavailable or not fully functional (for Ghana, Peru, India, and Mexico). Local data on breast cancer epidemiology, survival, and breast cancer stage distributions were derived from different sources, although often from composite hospital data from the (urban) public sector. Likewise, practice and unit cost variation are very likely within our analyzed countries and were also often derived from the public sector. For example, within Peru, there are noticeable variations in breast cancer treatment procedures, which differed by hospital or health maintenance organization. Since our data is based on patients and practices in urban areas and the public sector rather than on all patients, our cost-effectiveness estimates may not be representative of the whole country. As cancer registries provide essential information on the cancer burden, understanding the causes of cancer, the prospects for cancer control, and potentially costs, these limitations indicate the need to start national functional, population-based cancer registries in LMICs. Support could, for example, be offered by the Global Initiative for Cancer Registry Development [23,24].

Third, a key aspect in the WHO-CHOICE models applied in our cost-effectiveness studies is the relationship between early detection and improved breast cancer stage distributions (and eventual health outcomes). A proof of concept of the relationship between early detection strategies and breast cancer stage distribution is presented in Chapter three. However, there currently is no external validation of the proposed model in this chapter and it is therefore uncertain whether the model can be applied to LMICs. Also, in the relationship between early detection and breast cancer stage distribution we did not account for the effects of early detection strategies on (stage-specific) incidence rates.

Other modeling studies have indicated that the observed breast cancer incidence will significantly increase as a result of breast cancer screening, and this is likely also true for other early detection strategies. This increase in breast cancer incidence can be the result of diagnosing additional stage-I cancers, but it does not necessarily mean a reduction of the absolute numbers of stages III and IV cancers and, correspondingly, improved breast cancer stage distribution. The cost-effectiveness estimates presented in this thesis could therefore be biased and could be too optimistic in general. Despite these limitations, the results of our model show similarities with results from other models [8,25,26], and these limitations fit with our overall aim to inform general policy discussions by proving the broad cost-effectiveness indications of a range of comprehensive interventions. More precise estimates of the effectiveness of breast cancer screening interventions through more detailed breast cancer models are important [27,28]. This could, for example, be achieved by linking our detailed WHO-CHOICE costing estimates with the MISCAN model.

Fourth, a healthcare perspective has been used in the cost-effectiveness analyses in this thesis, and the travel costs or productivity losses of patients seeking or undergoing care were not included. The healthcare perspective is the most commonly used perspective in economic evaluations presented in this thesis. Including these costs would probably lead to increased costs and savings generally and different cost patterns [29]. Although cost-effectiveness analyses using a health care perspective contribute very important information, productivity losses for patients suffering from breast cancer (and, most likely, other non-communicable diseases) are substantial [29,30]. Previous studies have indicated that healthcare costs account for 45% of the total costs associated with breast cancer. Non-healthcare costs seem to be generally larger (about 55%) compared to healthcare costs since breast cancer commonly occurs in women during their reproductive lifespan, especially in LMICs [31,32]. Future research should be more inclusive by using a societal perspective and investigating productivity losses.

Fifth, the recommendations in the presented cost-effectiveness studies are subject to a hypothetical cost-effectiveness threshold that is not fully relevant in LMICs. The proposed threshold value is very generic (three times the GDP per capita per DALY) and does not apply to a specific context, to a specific moment in time, or under specific conditions. In reality, the threshold value is dynamic, and hence, the proposed cost-effectiveness threshold values should not be interpreted strictly. Although these thresholds can be still useful as a criterion in many decision-making processes, the results of cost-effectiveness studies should be presented in disaggregated form. Instead of concentrating on threshold values, future cost-effectiveness analyses should strive for transparency by presenting all input information used in a way that allows policymakers to verify the assumptions, view the uncertainties, and weigh the importance of the assumptions and uncertainties.

Sixth, as previously discussed, recommendations that are based solely on the cost-effectiveness of breast cancer interventions fall short to adequately inform policymakers. Future cost-effectiveness analyses should therefore be extended with broader types of analysis, such as MCDA. This broader approach could foster the broad acceptance of decisions and increase the likelihood that prioritized breast cancer control strategies will be implemented.

Concluding remarks

Breast cancer and other cancers affect many people worldwide. Breast cancer kills women, men, and even children and tears apart millions of families, particularly in LMICs. Because of a lack of access to early detection and treatment facilities, breast cancer is considered a death sentence in LMICs, and although much has been learned about the disease, little has been done for the thousands of women diagnosed each year with breast cancer in these countries. Women in LMICs could be saved if early detection linked to appropriate treatment were offered.

This thesis provides recommendations on the types of early detection and treatment strategies that should be provided in these countries. It suggests that CBE screening strategies (ages 40–69) are cost-effective and can be recommended for LMICs. Breast health awareness-raising is an important component, although it could also be an economically attractive early detection strategy in itself. Even though additional investments for implementing these early detection strategies can be substantial, the health benefits to society will generally outweigh the additional costs.

This thesis confirms that when criteria beyond affordability and cost-effectiveness are considered, CBE screening strategies should be given priority in LMICs and aromatase inhibitors could be provided in addition to essential treatment. Providing mammography screening, taxanes, and trastuzumab should be given less priority in LMICs.

However, such interventions in LMICs require a great deal of time and money, and there seems to be enormous distance between the goal of saving thousands of women suffering from breast cancer each year and the reality of the limited possibilities in LMICs. This thesis propagates the message that progress in breast cancer control in LMICs lies not in an extension of state-of-the-art interventions, but in the knowledge of the limitations that LMICs face. Small steps should be taken in the right direction, and affordable and comprehensible interventions such as breast health awareness-raising, CBE screening, surgery, radiotherapy and basic palliative care should be given first priority.

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Appendix of general discussion

Appendix Table A1. Criteria definitions, scoring scales and weights developed during the Colombian experiment.

			Intervention 1	Intervention 2
1. Number of potential beneficiaries				
Definition	Levels	Weight (as %)		
The number of people with the health condition that are eligible for the intervention. Per 100.000 of the Colombian populations.	0 <2 per 100.000 (per year)	0.0%		
	1 2 >< 5 per 100.000 (per year)	5.3%		
	2 5 >< 10 per 100.000 (per year)	9.1%		
	3 10 >< 15 per 100.000 (per year)	12.5%		
	4 > 15 per 100.000 in population per year)	16.7%		
2. Safety				
Definition	Levels	Weight (as %)		
Safety is the practical certainty that adverse effects to patients or providers will not result from exposure to an intervention under defined circumstances.	0 there is a risk of severe adverse effects (life threatening) to patients or a risk of adverse effects (of any kind) to providers	0.0%		
	1 there is a risk of mild adverse effects to patients and/or to providers.	10.0%		
	2 there is no risk or a risk of very mild adverse effects (adverse effects which will completely recover within a month) to patients and/or to providers	15.6%		
3. Cost-effectiveness				
Definition	Levels	Weight (as %)		
The capacity to produce the maximum output for a given monetary input.	0 not cost-effective (e.g. costs per gained healthy life year are above 3*Gross Domestic Product (GDP) per capita)	0.0%		
	1 cost-effective (e.g. costs per gained healthy life year are below 3*GDP per capita)	10.4%		
	2 highly cost-effective (e.g. costs per gained healthy life year are below 1*GDP per capita)	15.1%		
5. Effectiveness				
Definition	Size of the effect	Weight (as %)		
Effectiveness is the extent to which an intervention restores the health gap caused by the condition (e.g. the number of DALYs without the intervention/number of DALYs with the intervention)	0 less effective (e.g. < 5% reduction of DALYs in a single patient)	0.0%		
	1 Moderate (e.g. 5><10% reduction of DALYs in a single patient)	6.9%		
	2 Very effective (e.g. >10% reduction of DALYs in a single patient)	12.2%		

			Intervention 1	Intervention 2
6. Geographical coverage/area of living				
Definition	Levels	Weight (as %)		
The ability of the intervention to be reached by the target population, independent of their living place or income (includes out of pocket expenditures)	0 the intervention does not cover or is too expensive to reach, for (most) people who live outside cities. More than 20% of the Colombian population	0.0%		
	1 the intervention does not cover or is too expensive to reach, for some people who live outside cities. Between 10% and 20% of the Colombian population	5.0%		
	2 the intervention covers (almost) all people in Colombia	11.3%		
7. Severity of the health condition of patients targeted by intervention				
Definition	Levels	Weight (as %)		
The degree to which the condition affects a person's health lifetime by causing death, handicap, disability, any kind of suffering or pain. This includes emotional, mental, social and/or physiological factors for both the patient and her family	0 not severe (healthy or including risk factors)	0.0%		
	1 severe (e.g. stage I or II breast cancer)	5.7%		
	2 very severe advanced breast cancer (e. g. stage III or IV breast cancer)	8.3%		
8. Technical complexity				
Definition	Ability to train and deliver all clinical and organizational requirements to run the intervention.	Weight (as %)		
Other types of inputs required in addition to monetary inputs to implement and to keep providing the intervention (These include human resource requirements, both quantitative and qualitative, and organizational requirements. The potential to integrate the intervention into an already existing health system should also be taken into account).	0 poor ability	0.0%		
	1 moderately good ability	4.5%		
	2 good ability	8.3%		

Summary

Life is not always a matter of holding good cards,

but sometimes of playing a poor hand well

Thesis rationale

Breast cancer and other cancers are now leading causes of death and disability in low- and middle-income countries (LMICs). Although cancers were thought to be a problem almost exclusive to high-income countries (HICs), the breast cancer incidence is increasing in LMICs and the associated mortality is relatively high. While LMICs now bear the majority of the burden of breast cancer, their health systems are predominantly ill prepared to meet this challenge and there is an urgent need to identify cost-effective and affordable breast cancer control strategies in LMICs.

HICs have made major improvements in the fight against breast cancer, particularly in the past three decades. Much is known about the disease, and there has been a substantial increase in medical interventions, mostly in HICs, where more resources and infrastructure are available. Both breast cancer incidence and mortality have declined in HICs because of these interventions, which include enhanced awareness of signs and symptoms, earlier detection, and the availability of new and more effective treatment. Women in HICs who are diagnosed with breast cancer in an early stage of the disease can now reasonably expect to be cured and to live a disease-free life.

Although much has been learned about breast cancer, little has been done for the thousands of women diagnosed with breast cancer each year in LMICs, where the disease is still considered a death sentence. These women could be saved if early detection linked to appropriate treatment were offered. However, this requires a well-functioning health system, skilled personnel, and modern equipment, and the interventions available in HICs cannot simply be realized in LMICs. Because of the different dynamics in population and the epidemiology of breast cancer, the relative effectiveness of these interventions is also unknown in LMICs. Moreover, the costs of breast cancer control interventions are a major constraint, adding to the complex discussion on how best to control the disease in LMICs.

Cost-effectiveness analysis (CEA) systematically compares the costs and effects of health interventions and can be a useful guiding tool in health care spending. CEAs can assist policymakers in LMICs with their decisions on national breast cancer control strategies by identifying which interventions provide the greatest value for money. This information is particularly important in LMICs, which often have fragile health systems and lack sustainable resources. Since this information is currently insufficient, the general objective of this thesis is to improve the knowledge base for the cost-effectiveness of interventions for breast cancer control in LMICs.

This thesis addresses a single research question (Chapter one) to reach this objective: What is the cost-effectiveness of a range of breast cancer control interventions along the continuum of care in a number of LMICs?

To answer this research question, this thesis presents eight scientific studies. This thesis first provides a systematic review of available cost-effectiveness estimates for breast cancer control in LMICs (Chapter two). It then demonstrates a method to predict the stage distribution of different breast cancer screening options, which can be used to estimate the effectiveness of screening interventions (Chapter three). Four case studies are then presented that provide the costs, effects, and cost-effectiveness information of breast cancer control interventions in Ghana, Peru, Mexico, Costa Rica, and India (Chapters four to seven). More global cost-effectiveness estimates are presented in Chapter eight. To comprehensibly guide LMICs in improving breast cancer control, this thesis also focuses on other considerations next to cost-effectiveness. The last scientific study in this thesis therefore reflects on multiple relevant criteria, including cost-effectiveness, to support comprehensive breast cancer control strategies in LMICs (Chapter nine). These studies are discussed together in Chapter ten of this thesis.

Interventions that provide the greatest health for money: Contributions of this thesis

This thesis starts with a systematic review on available cost-effectiveness estimates for breast cancer control in LMICs (Chapter Two). Our review confirms that few health economic studies on breast cancer control have been conducted in LMICs and that this type of research in LMICs is still in its infancy. The results indicate the need for more economic analyses that are uniform and of better quality, analyses that cover a comprehensive set of interventions and result in clear policy recommendations. The review identified 24 economic studies that evaluated different kinds of screening, diagnostic, and therapeutic interventions in various age and risk groups in LMICs. Of these 24 studies, only seven presented functional cost-effectiveness results (from which cost-effectiveness ratios could be determined). These studies suggest that radiotherapy and surgery are very cost-effective ($233 and $351 per life-year saved, respectively) and that screening strategies may be economically attractive in LMICs (i.e., in India and Mexico, but not Morocco). However, these studies present very little evidence upon which to provide specific recommendations (on screening by mammography vs. clinical breast examination, the frequency of screening, or the target population).

As the current knowledge on the costs and effects of breast cancer control strategies in LMICs is limited, it is uncertain how early detection strategies will perform and how much they will cost in a specific LMIC. Chapter three therefore demonstrates a theoretical method to predict the stage distribution of different breast cancer screening options in LMICs. The amount of stage shift is an essential early detection indicator and an important proxy for the performance of screening programs and their possible further impact. The model can (in theory) be used to estimate the potential effect on the stage distribution of screening interventions in LMICs, and it uses default estimates for indicators such as attendance rates and sensitivity rates. The results of this chapter show that our model can be used to estimate the stage shifts of the Nijmegen Screening Program and provides proof of concept that it could also be adapted to other settings with different characteristics. Using hands-on data and formulas (i.e., y =0.45 + 0.9349*index Z), this model could provide important information on the performance of the breast cancer screening programs that LMICs consider implementing.

Chapter four presents a case study performed in Ghana. Studies on breast cancer in Ghana typically report poor stage distribution, survival, and awareness of breast cancer symptoms. The knowledge, beliefs, and social stigma of Ghanaians are important determinants of the late-stage presentation of breast cancer. These poor conditions highlight the need to improve breast cancer control policy in Ghana and address the needs of Ghana's relatively young female population. Our analysis suggests that to be efficient, breast cancer control in Ghana should be oriented toward earlier detection. Biennial screening by clinical breast examination (CBE) of women aged 40–69 years, in combination with treatment of all stages, seems to be the most cost-effective intervention (costing $1,299 per DALY averted). Mass media awareness-raising (MAR) is the second-best option (costing $1,364 per DALY averted). Mammography screening of women aged 40–69 years (costing $12,908 per DALY averted) cannot be considered cost-effective.

Another case study was performed in Peru (Chapter five), where breast cancer has shown a persistent increase in incidence over the last decades and where many women present in advanced breast cancer stages. This detailed case study indicates that triennial screening strategies are the most cost-effective in Peru, particularly when a combination of fixed and mobile mammography screening is applied (from $4,125 per DALY averted). However, because of its high budget impact and challenging implementation characteristics, a combination of fixed and mobile mammography screening will only be preferable when Peru's economic and health system conditions improve. CBE screening with upfront fine needle aspiration (FNA) in non-urban settings (age 40–69), combined with both CBE and fixed mammography screening in urban settings (age 40–69) could be a cost-effective and more feasible option for Peru in the near future (from $4,239 per DALY averted). Late-stage treatment, trastuzumab therapy, and annual screening strategies are the least cost-effective in Peru.

Chapter six reports on our analysis in Costa Rica and Mexico, two Central American countries. To improve their current breast cancer control programs, our analysis suggests that both Costa Rica and Mexico would benefit from implementing strategies that advance early detection. In Costa Rica, the current strategy of treating breast cancer in stages I to IV at an 80% coverage level seems to be the most cost-effective ($4,739 per DALY averted). CBE screening could improve Costa Rica's population health twofold and can would be very cost-effective ($5,964 per DALY averted). For Mexico, our results indicate that a mass media awareness raising program (MAR) could be most cost-effective ($5,021 per DALY averted). If more resources become available in Mexico, biennial mammography screening for women (age 50–70) would be recommended ($12,718 per DALY averted).

Breast cancer is an emerging public health problem in India and already causes a high burden of disease in this country. Costs of breast cancer treatment play an increasingly important role in India, as 59% of the total expenditure on health care is paid out of pocket. The largest costs are represented by drugs for systemic treatment; these are less accessible to Indian breast cancer patients. Thus, in Chapter seven, this thesis focused only on the impact of systemic drug prices on cost-effectiveness. This information can be used for drug price reductions to make breast cancer treatment more cost-effective and accessible. The results of this study suggest that AC[1] or CMF[1] chemotherapy regimes, combined with tamoxifen, can be cost-effective in India (from $1,840 per DALY averted). When more resources become available for breast cancer control in India, CAF[1] combined with tamoxifen could be considered for implementation, as their ICERs are only slightly above the suggested threshold value ($5,102 per DALY averted). Trastuzumab prices need to decrease fifty-fold to be considered cost-effective in India.

Chapter eight reports on the cost-effectiveness of interventions to combat breast, cervical, and colorectal cancers in two world sub-regions with very high adult and child mortality. This study takes a wider (sectoral) and more global perspective and finds that a number of highly cost-effective interventions to combat cervical and colorectal cancer are available in Sub-Saharan Africa (AFR-E) and Southeast Asia (SEAR-D). For cervical cancer, these include screening through Pap smears or visual inspection with acetic acid in combination with treatment (from I$142 per DALY averted). For colorectal cancer, increasing treatment coverage is highly cost-effective (below I$2,000 per DALY averted). For breast cancer control, mammography screening in combination with treatment of all stages is cost-effective (I$2,248–4,596 per DALY averted). It seems that screening for breast cancer control is relatively more cost-effective than screening for colorectal cancer but less cost-effective than cervical cancer screening.

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[1] *AC = cyclophosphamide and doxorubicin; CMF = cyclophosphamide, methotrexate, fluorouracil; CAF = cyclophosphamide ,doxorubicin and fluoracil*

When the study in chapter eight is extended to all 14 world sub-regions, rough global cost-effectiveness ratios can be estimated (Chapter ten). These estimates can be used as a starting point for countries for which country-specific estimates are currently unavailable. Treatment of stage I, II, III, and IV breast cancer only about $558, $1,011, $2,864, and $26,850 per DALY averted, respectively. Globally, late-stage breast cancer management (stages III and IV) is twice as expensive as early-stage breast cancer management (stages I and II). Treatment of all stages comes at a global cost of roughly $2,260 per DALY averted. Early detection strategies trough breast health awareness raising costs $2,297 (BAR) and $1,555 (MAR) per DALY. Population-based screening costs of $1,146 (biennial CBE), $1,071 (triennial CBE), $1,398 (triennial mammography), and $1,574 (biennial mammography) per DALY averted.

If only treatment were available worldwide and early detection strategies were absent, the number of DALYs saved would be about three per breast cancer patient. When, next to treatment, early detection strategies are implemented, the number of DALYs may increase threefold, to about 10 per breast cancer patient. Although additional investments for implementing early detection strategies can be substantial and may double breast cancer control expenditures, the health benefits to society that would accrue from these strategies would outweigh the additional costs. The average cost per unit of health will decrease because of early detection, allowing resources to be allocated more efficiently.

Interventions that provide the greatest value for money: Implications for policymakers

Whether to choose MAR, CBE screening, mammography screening, or mixed screening for early detection in a specific LMIC or whether to provide aromatase inhibitors, taxanes, or trastuzumab, seems to depend on the many country-specific inputs that define the cost-effectiveness of these interventions. CBE screening strategies (ages 40–69) seem to be cost-effective in most LMICs and mammography screening (ages 50–69) seems to be cost-effective only in those countries with sufficient resources (GDP per capita over $4,000). Early detection linked to essential treatment (surgery, radiotherapy, AC chemotherapy, tamoxifen) seems to be cost-effective in all LMICs and could be complemented with aromatase inhibitors. Providing taxanes or trastuzumab is generally not economically attractive unless LMICs have a GDP per capita over $6,000 or $8,000, respectively.

Information from CEAs may help governments select breast cancer control strategies to maximize health benefits. However, policymakers often deviate from CEA results because of other principles that are valuable to society. National breast cancer control programs should therefore not only be based on interventions that provide the greatest health for money but on those that provide the greatest value for money. This means maximizing the utility of breast cancer control programs on the basis of a broader trade-off process that includes all valuable criteria. This type of approach is called multi-criteria decision analysis (MCDA); Chapter nine of this thesis explored a range of considerations for selecting breast cancer control strategies with international experts. The results from this study confirm that effectiveness, quality of the evidence, magnitude of individual health impact, acceptability, cost-effectiveness, technical complexity, affordability, safety, geographical coverage, and accessibility are also important. Furthermore, a rating tool for policy makers to prioritize breast cancer interventions is proposed in this study.

To demonstrate the use of this rating tool, a short implementation experiment was performed in Colombia (Chapter ten). The value for money of fifteen Colombian breast cancer control interventions was estimated based on eight relevant criteria: cost-effectiveness, number of potential beneficiaries, safety, acceptability, effectiveness, geographical coverage, severity of the health condition, and technical complexity. This proposed MCDA approach could be more realistic, integrated, and useful in practice for decisions on breast cancer control. The most value for money is provided by aromatase inhibitor therapy or switch therapy in early-stage breast cancer. With regard to early detection interventions combined with treatment, biennial CBE screening in women aged 40–49 provides the most value for money. Triennial CBE screening in women aged 40–49 combined with mammography screening in women aged 50–69 is the second-best option for early detection in Colombia.

Conclusions

In an effort to reduce the high number of breast cancer deaths in LMICs, this thesis provides careful recommendations on the types of early detection and treatment strategies that should be provided in these countries. It finds that CBE screening strategies (ages 40–69) are cost-effective and can be recommended for LMICs. In this, breast health awareness raising is an important component, although it could also be an economically attractive early detection strategy in itself. Even though additional investments for implementing early detection strategies can be substantial, the health benefits to society will generally outweigh the additional costs and resources are allocated more efficiently.

When, in addition to affordability and cost-effectiveness, other criteria are considered simultaneously, this thesis confirms that CBE screening strategies should be given priority in LMICs and that aromatase inhibitors could be provided in addition to essential treatment. Providing mammography screening, taxanes, or trastuzumab should be given less priority in LMICs.

Nevertheless, all breast cancer control components - early detection, diagnosis, treatment, follow-up and palliative care - should be made available in LMICs because they are essential for the functioning of the breast cancer control program. If access to any of these components is lacking or if proper referral systems between these components are lacking, the quality and effectiveness of breast cancer control will decrease. This leaves societies in LMICs with the challenge of synchronously improving all these essential control components and keeping breast cancer services accessible to those who need them. These improvements require a great deal of time and money and are thus especially challenging for LMICs.

Thus there seems be a distance between the goal of saving thousands of women suffering from breast cancer each year and the reality of the limited possibilities in LMICs. Small steps should be taken in the right direction, and affordable and comprehensible interventions, such as breast health awareness-raising, CBE screening, surgery, radiotherapy and basic palliative care should first be given priority. ***Life is not always a matter of holding good cards, but sometimes of playing a poor hand well.*** The global community should now support these small steps, as the futures of many women living in LMICs and their families depends on what we do today.

Samenvatting

Life is not always a matter of holding good cards,

but sometimes of playing a poor hand well

Aanleiding van dit proefschrift

Borstkanker en andere vormen van kanker zijn een belangrijke oorzaak van ziekte en sterfte in lage- en middeninkomenslanden (LMIL's). Hoewel kanker altijd is gezien als een probleem van hoge inkomenslanden (HIL's), is het aantal borstkankergevallen in LMIL's inmiddels fors toegenomen en is de sterfte aan borstkanker in deze landen onevenredig hoog. Tegenwoordig kennen LMIL's daarmee de grootste ziektelast door borstkanker, maar zijn de gezondheidszorgsystemen in deze landen slecht voorbereid op de uitdagingen die deze ziekte stelt. Het is daarom de hoogste tijd dat deze landen kosteneffectieve en betaalbare strategieën voor het bestrijden van borstkanker vaststellen.

De HIL's, waar meer financiële middelen en voorzieningen aanwezig zijn, hebben in de afgelopen drie decennia al grote sprongen vooruit kunnen maken in de strijd tegen borstkanker. Men is veel over de ziekte te weten gekomen en sindsdien is er een substantiële toename van medische interventies geweest. Door deze medische interventies, zoals onder andere het verbeteren van het bewustzijn van borstkankersignalen en symptomen, vroegtijdige opsporing, en het beschikbaar komen van verbeterde behandelmethoden, zijn zowel het aantal nieuwe borstkankergevallen en de sterfte aan borstkanker afgenomen. Vrouwen in HIL's die de diagnose borstkanker krijgen in een vroegtijdig stadium, mogen tegenwoordig redelijkerwijs genezing van de ziekte verwachten.

Hoewel er veel kennis is vergaard over borstkanker, is er nog maar erg weinig gedaan voor de duizenden vrouwen die ieder jaar de diagnose borstkanker krijgen in LMIL's, waar de ziekte nog steeds als een doodstraf geldt. Deze vrouwen kunnen worden gered van een gewisse dood als zou worden voorzien in een vroegtijdige opsporing gelinkt aan passende behandelingen. Echter, dit vereist een goed functionerend gezondheidszorgsysteem, competent personeel en moderne voorzieningen. De in HIL's beschikbare interventies om borstkanker te bestrijden, kunnen niet zomaar in LMIL's worden geïmplementeerd. Gezien de populatiedynamiek en de epidemiologie van borstkanker anders zijn in HIL's, is de relatieve effectiviteit van deze interventies onbekend in LMIL's. Bovendien kunnen de kosten van deze interventies een groot struikelblok vormen voor LMIL's. Naast de overwegingen ten aanzien de effectiviteit van borstkankerinterventies, moeten kostenoverwegingen absoluut worden toegevoegd aan de lijst met lastig af te wegen criteria omtrent borstkankerbestrijding in LMIL's.

In kosteneffectiviteitsanalyses (KEA's), worden de kosten en effecten van interventies systematisch vergeleken. KEA's kunnen daarom een erg nuttig en sturend instrument zijn in beslissingen rondom gezondheidszorguitgaven. KEA's kunnen beleidsmakers in LMIL's handvatten bieden voor beslissingen rondom borstkankerbestrijding, omdat ze de interventies aanwijzen die het meeste rendement (***value for money***) genereren. Juist in LMIL's is deze informatie belangrijk, omdat deze landen vaak zeer fragile gezondheidszorgsystemen en een structureel gebrek aan financiële middelen hebben.

Omdat de informatie ten aanzien van de kosten en effecten van borstkankerbestrijding op dit moment ontbreekt, is dit proefschrift gericht op het vergroten van de kennis over de kosteneffectiviteit van borstkankerbestrijding in LMIL's. Dit proefschrift richt zich derhalve op één onderzoeksvraag (hoofdstuk één): Wat is de kosteneffectiviteit van een aantal borstkankerbestrijdingsinterventies binnen het complete zorgcontinuüm, in een reeks LMIL's?

Er worden in dit proefschrift acht wetenschappelijke studies gepresenteerd om deze onderzoeksvraag te beantwoorden. Allereerst wordt er een systematisch overzicht gegeven van de reeds beschikbare kosteneffectiviteitschattingen van borstkankerbestrijdingsinterventies in LMIL's (hoofdstuk 2). Vervolgens wordt er een methode gepresenteerd om de stadiumdistributie van borstkanker te voorspellen, in het kader van verschillende opties voor borstkankerscreening (hoofdstuk 3). In hoofdstuk vier tot en met zeven worden vier casestudies beschreven met informatie over de kosten, effecten en kosteneffectiviteit van borstkankerbestrijdingsinterventies in Ghana, Peru, Mexico, Costa Rica en India. Meer globale kosteneffectiviteitsschattingen worden vervolgens aangeboden in hoofdstuk acht. Om LMIL's op een allesomvattende manier te helpen met een verbetering van de borstkankerbestrijding, gaat dit proefschrift ook in op andere criteria naast kosteneffectiviteit. De laatste wetenschappelijke studie in dit proefschrift reflecteert daarom op meerdere relevante criteria voor het verbeteren van borstkankerbestrijdingsstrategieën in LMIL's, waarvan kosteneffectiviteit er één van is (hoofdstuk 9). Alle bovenstaande studies worden gezamenlijk bediscussieerd in hoofdstuk 10.

Interventies die het meeste gezondheidsrendement (health for money) opleveren: bijdragen van dit proefschrift

Hoofdstuk twee van dit proefschrift geeft een systematisch overzicht van reeds beschikbare kosteneffectiviteitsschattingen voor borstkankerbestrijding in LMIL's (hoofdstuk 2). Het systematische overzicht bestaat uit 24 economische studies die verschillende soorten screening, diagnostische en therapeutische interventies evalueerden in LMIL's, binnen een verscheidenheid aan leeftijdsgroepen en risicogroepen. Uit slechts zeven van deze 24 studies konden functionele kosteneffectiviteitsresultaten worden afgeleid. Deze zeven studies suggereerden dat radiotherapie en chirurgie zeer kosteneffectief zijn (respectievelijk $233 en $351 per gewonnen levensjaar) en dat borstkankerscreening economisch aantrekkelijk kan zijn in LMIL's (wel in India en Mexico, maar in Marokko niet).

Deze studies leverden echter weinig bewijs op om specifieke aanbevelingen te doen voor borstkankerscreening in LMIL's. Zo is het niet duidelijk of mammografie dan wel klinisch borstonderzoek (KBO) moet worden ingezet, of wat de frequentie van screening of de leeftijd van de doelpopulatie in deze landen moet zijn. Het overzicht bevestigt het heersende beeld dat er maar erg weinig gezondheids-economische studies op het gebied van borstkankerbestrijding in LMIL's zijn uitgevoerd, en ook dat dit type onderzoek nog in de kinderschoenen staat. Deze resultaten geven de noodzaak weer om meer economische studies uit te voeren in LMIL's die meer uniform en van betere kwaliteit zijn. Daarnaast zouden deze studies een meer uitgebreide reeks aan interventies moeten analyseren en ook concretere beleidsboodschappen moeten genereren.

Gezien het feit dat de huidige kennis ten aanzien van de kosten en effecten van borstkankerbestrijdingsstrategieën beperkt is, blijft het onduidelijk wat de impact is van de vroegtijdige opsporing van borstkanker in LMIL's en wat dit kost. In hoofdstuk drie leggen we daarom een theoretische methode voor om de stadiumdistributie, ten gevolge van verschillende borstkankerscreeningsopties, in LMIL's te voorspellen. De mate van verandering in stadiumdistributie (stage shift) is een essentiële graadmeter in de vroegtijdige opsporing van borstkanker. Bovendien is deze stage shift een belangrijke voorwaarde voor het slagen van screeningsprogramma's en hun mogelijke verdere impact. In theorie kan de voorgestelde methode worden gebruikt om het potentiele effect van screeningsinterventies op de stage shift in LMIL's te schatten. Het model gebruikt ook waardevolle standaardwaarden, zoals waarden voor de opkomst en sensitiviteit van een screeningsprogramma, die ook gebruikt kunnen worden in andere studies. De resultaten van dit hoofdstuk laten zien dat ons model gebruikt kan worden om de stage shift van het Nijmeegse screeningsprogramma te bepalen, en laten daarnaast conceptueel bewijs zien dat het model ook gebruikt kan worden in landen met andere karakteristieken. Met direct te gebruiken data en formules (y =0.45 + 0.9349*index Z), kan ons model belangrijke informatie verschaffen wat betreft het potentiële vermogen van screeningsprogramma's die LMIL's overwegen in te zetten in de strijd tegen borstkanker.

Hoofdstuk vier van dit proefschrift beschrijft een casestudy die uitgevoerd is in Ghana. Studies naar borstkanker in Ghana typeren zich door het rapporteren van een slechte stadiumdistributie, slechte overlevingskansen en een laag bewustzijn ten aanzien van borstkankersignalen en symptomen. De kennis, overtuigingen en het sociale stigma van Ghanezen zijn belangrijke determinanten voor het late stadium waarin vrouwen met borstkanker zich presenteren. Deze slechte omstandigheden onderstrepen de noodzaak het borstkankerbeleid in Ghana te verbeteren en te voorzien in de behoeften van de relatief jonge, vrouwelijke bevolking van Ghana. Onze analyse suggereert dat, om efficiënt te zijn, borstkankerbestrijding in Ghana gericht moet worden op vroegtijdige opsporing van de ziekte. Tweejaarlijkse screening door middel van klinisch borstonderzoek (KBO) van vrouwen van 40 tot en met 69 jaar, in combinatie met de behandeling van alle borstkanker gevallen, lijkt de meest kosteneffectieve interventie ($ 1,299 per vermeden Disablity Adjusted Life Year [DALY]).

Bewustmaking door middel van massamedia daarna de beste optie ($ 1,364 per vermeden DALY). Screening van vrouwen in de leeftijdsgroep 40-69 door middel van mammografie kan niet beschouwd worden als kosteneffectief ($ 12,908 per vermeden DALY).

De volgende casestudy is uitgevoerd in Peru (hoofdstuk vijf). Peru is een land waarin een hardnekkige groei van het aantal borstkankergevallen zichtbaar is geworden in de afgelopen decennia, en waar veel vrouwen in een laat stadium gediagnosticeerd worden. Deze gedetailleerde casestudy geeft aan dat driejaarlijkse screeningsstrategieën het meest kosteneffectief zijn in Peru, vooral wanneer een combinatie van vaste en mobiele mammografie units wordt ingezet (vanaf $4,125 per vermeden DALY). Echter, door de hoge budgetvereisten en de uitdagende implementatie, zullen combinaties van vaste en mobiele mammografie-screeningsstrategieën pas aan te bevelen zijn wanneer de economische- en gezondheidszorgvoorwaarden van Peru verbeterd zijn. In de nabije toekomst zou een meer kosteneffectieve en haalbare optie voor Peru zijn: KBO screening voorafgaand met fijne naald aspiratie (FNA), in niet-stedelijke gebieden (leeftijdsgroep 40-69). Dit in combinatie met zowel KBE en vaste mammografie units in stedelijke gebieden (leeftijdsgroep 40-69). Het minst kosteneffectief in Peru zijn behandelingen met trastuzumab, het behandelen van patiënten in late stadia, of jaarlijkse screeningsstrategieën.

Hoofdstuk zes van dit proefschrift heeft betrekking op onze analyses in Costa Rica en Mexico. De analyses suggereren dat, om de huidige borstkankerbestrijdingsprogramma's van deze landen te verbeteren, zowel Costa Rica en Mexico zouden kunnen profiteren van strategieën die de vroegtijdige opsporing van borstkanker bevorderen. In Costa Rica lijkt de huidige strategie, de behandeling van borstkanker in stadium I tot en met IV bij een 80% dekkingsgraad, het meest kosteneffectief te zijn ($ 4,739 per vermeden DALY). KBO screening zou de gezondheid van Costa Rica's borstkanker patiënten echter kunnen verdubbelen en dit zou nog steeds zeer kosteneffectief zijn ($ 5,964 per vermeden DALY). Onze resultaten laten zien dat voor Mexico mogelijk een massamediale bewustmakingscampagne het meest kosteneffectief is ($ 5,021 per vermeden DALY). Als in de toekomst meer financiële middelen beschikbaar zouden komen in Mexico, kan tweejaarlijkse mammografiescreening voor vrouwen (leeftijdsgroep 50-70) worden aanbevolen ($ 12,718 per vermeden DALY).

Borstkanker is ook een opkomend probleem in India en veroorzaakt al een hoge ziektelast in dit land (hoofdstuk zeven). Kosten van de behandeling van borstkanker spelen een steeds belangrijkere rol in India, gezien 59% van de totale uitgaven aan gezondheidszorg wordt betaald door patiënten zelf (out of pocket). De grootste kostenpost voor borstkanker wordt bepaald door medicijnen voor systemische behandeling. Deze medicijnen zijn dan ook minder toegankelijk voor Indiase borstkankerpatiënten. In hoofdstuk zeven van dit proefschrift richten we ons daarom op de invloed van prijzen van systemische geneesmiddelen op de kosteneffectiviteit van borstkankerbehandelingen in India. Deze informatie zou kunnen worden gebruikt om de medicijnprijzen voor het behandelen van borstkanker te reduceren, ze meer toegankelijk en kosteneffectief te maken.

De resultaten van deze casestudy geven aan dat AC[1] of CMF[1] chemotherapie kuren, gecombineerd met tamoxifen, kosteneffectief zijn in India (vanaf $ 1,840 per vermeden DALY). Als er meer financiële middelen beschikbaar komen voor borstkankerbestrijding in India, kan CAF[1] gecombineerd met tamoxifen overwogen kunnen worden voor implementatie ($ 5,102 per vermeden DALY). Trastuzumab prijzen moeten wel 50 keer goedkoper worden eer ze beschouwd kunnen worden als kosteneffectief in India.

In hoofdstuk acht behandelen we de kosteneffectiviteit van interventies voor de bestrijding van borstkanker, baarmoederhalskanker en dikke darmkanker. Deze studie is uitgevoerd voor Sub-Sahara Afrika (AFR-E) en Zuidoost-Azië (SEAR-D), twee sub regio's van de wereld met een hoge kind- en volwassenensterfte. Dit onderzoek heeft, in vergelijking met de andere casestudies in dit proefschrift, een breder (sectoraal) en mondialer perspectief en laat zien dat er een aantal zeer kosteneffectieve interventies voor het bestrijden van kanker beschikbaar zijn in de onderzochte sub-regio's. Voor baarmoederhalskanker is screening door middel van uitstrijkjes of visuele inspectie met azijnzuur, in combinatie met behandeling, zeer kosteneffectief (vanaf I$ 142 per vermeden DALY). Voor dikke darmkanker is het uitbreiden van de dekking van behandelingen zeer kosteneffectief (minder dan I$ 2,000 per vermeden DALY). Voor borstkanker blijkt mammografiescreening in combinatie met de behandeling van alle stadia kosteneffectief te zijn (I$ 2,248-4,596 per vermeden DALY). Uit deze studie blijkt dat borstkankerscreening relatief kosteneffectiever is dan dikke darmkankerscreening, maar minder kosteneffectief dan baarmoederhalskankerscreening.

In hoofdstuk 10 is de analyse uit hoofdstuk acht uitgebreid naar alle 14 wereld sub-regio's en zijn grove kosteneffectiviteitsratio's geschat. Deze schattingen kunnen gebruikt worden als uitgangspunt voor landen waarvoor nauwkeurige schattingen op dit moment niet beschikbaar zijn. Uit onze analyses blijkt dat het behandelen van stadium I, II, III en IV borstkanker wereldwijd respectievelijk ongeveer $558, $1,011, $2,864, en $26,850 per vermeden DALY kost. De behandeling van borstkanker patiënten in een laat stadium (stadium III en IV) kost twee tot drie keer zoveel als het behandelen van patiënten in een vroeg stadium van de ziekte (stadium I en II). Het behandelen van alle stadia kost wereldwijd ongeveer $2,260 per vermeden DALY. Strategieën voor het vroegtijdig opsporen van borstkanker met behulp van bewustwordingscampagnes kosten ongeveer $2,297 (***basic awareness raising***) and $1,555 (***mass-media awareness raising***) per vermeden DALY. Het screenen van populaties op borstkanker kost ongeveer $1,146 (tweejaarlijkse KBO), $1,071 (driejaarlijkse KBO), $1,398 (driejaarlijkse mammografie) en $1,574 (tweejaarlijkse mammografie) per vermeden DALY.

1 AC = cyclofosfamide en doxorubicine; CMF = cyclofosfamide, methotrexaat, fluorouracil; CAF= cyclofosfamide, doxorubicine en fluorouracil

Als er alleen borstkankerbehandeling beschikbaar zou zijn in de wereld zijn en er geen vroegtijdige opsporingsstrategieën aanwezig zouden zijn, dan zou het aantal vermeden DALYs per borstkankerpatiënt ongeveer op drie uitkomen. Als hieraan een vroegtijdige opsporingsstrategie zouden worden toegevoegd, zou het aantal vermeden DALYs in drievoud toenemen naar ongeveer 10 per patiënt. Hoewel investeringen in het vroegtijdig opsporen van borstkanker aanzienlijk kunnen zijn en hierdoor de uitgaven aan borstkankerbestrijding kunnen verdubbelen, wegen de voordelen voor de gezondheid die voortvloeien uit vroegtijdige opsporing op tegen de extra investeringskosten. Er kan dus wereldwijd worden vastgesteld dat door vroegtijdige opsporing van borstkanker, de gemiddelde kosten per gezondheidseenheid omlaag worden gebracht en het geld efficiënter wordt besteed.

Interventies die het meeste waarde rendement (value for money) opleveren: implicaties voor beleidsmakers

Het kiezen van massamedia campagnes, KBO screening, mammografiescreening voor de vroegtijdige opsporing van borstkanker, of het kiezen van aromataseremmers, taxanen, of trastuzumab voor borstkanker behandeling, lijkt af te hangen van de vele specifieke karakteristieken die LMIL's hebben. Deze land-specifieke karakteristieken bepalen in grote mate de kosteneffectiviteit van borstkankerbestrijdingsinterventies. Zo lijkt in de meeste LMIL's KBO screening (leeftijdsgroep 40-69) het meest kosteneffectief te zijn en lijkt mammografiescreening (leeftijdsgroep 50-69) alleen kosteneffectief te zijn in landen met voldoende financiële middelen (BBP per inwoner meer dan $ 4,000). Vroegtijdige opsporingsstrategieën gekoppeld aan essentiële behandeling (chirurgie, radiotherapie, AC chemotherapie, tamoxifen) lijkt kosteneffectief te zijn in alle LMIL's en hier kunnen eventueel, afhankelijk van het beschikbare budget van het land, kuren met aromataseremmers aan worden toegevoegd. Het verstrekken van taxanen of trastuzumab is over het algemeen niet economisch aantrekkelijk, tenzij het BBP per inwoner van een LMIL meer telt dan respectievelijk $ 6,000 of $ 8,000.

Informatie van KEA's kunnen overheden helpen om borstkankerbestrijdingsstrategieën te kiezen op basis van gezondheidsrendement (health for money). Beleidsmakers wijken echter vaak af van de resultaten van KEA's, vanwege andere basisprincipes die waarde hebben voor de samenleving die ze vertegenwoordigen. Borstkankerbestrijdingsstrategieën moeten daarom niet alleen maar bestaan uit interventies die zorgen voor het meeste gezondheidsrendement, maar bestaan uit interventies die het meeste waarde-rendement genereren (value for money). De waarde van borstkankerbestrijdingsprogramma's zou eigenlijk gemaximaliseerd moeten worden op basis van een breder afwegingsproces, dat rekening houdt met alle existerende, waardevolle criteria in de samenleving. Dit proces wordt ook wel een multi-criteria besluitvormingsanalyse (MCBA) genoemd.

In hoofdstuk negen van dit proefschrift zijn daarom met internationale experts een aantal criteria voor het kiezen van borstkankerbestrijdingsstrategieën onderzocht. De resultaten van deze studie bevestigen dat er, naast kosteneffectiviteit, andere belangrijke criteria een rol spelen het afwegingsproces, namelijk: effectiviteit, sterkte van het bewijs, omvang van de individuele gezondheidswinst, aanvaardbaarheid, kosteneffectiviteit, technische complexiteit, betaalbaarheid, veiligheid, geografische dekking en toegankelijkheid. Om borstkankerinterventies te kunnen prioriteren op hun volledige waarde-rendement, is er ook een waarderingsinstrument voor beleidsmakers ontwikkeld in deze studie.

Om het gebruik van dit waarderingsinstrument te testen is er bovendien een kort onderzoek in Colombia uitgevoerd (hoofdstuk 10). Tijdens dit onderzoek zijn de kosten-waardeverhoudingen van vijftien Colombiaanse borstkankerbestrijdingsinterventies geschat, op basis van acht relevante criteria (kosteneffectiviteit, aantal begunstigden, veiligheid, aanvaardbaarheid, effectiviteit, geografische dekking, ernst van de gezondheidstoestand, en technische complexiteit). Deze MCBA aanpak zou tot meer realistische, geïntegreerde en praktisch bruikbare beslissingen over borstkankerbestrijding kunnen leiden. Uit dit onderzoek blijkt dat het meeste waarde-rendement kan worden toegekend aan behandeling in een vroeg stadium van borstkanker met aromataseremmers of switch therapie. Wat betref vroegtijdige opsporingsinterventies gecombineerd met behandeling, biedt tweejarige KBO screening (vrouwen 40-69 jaar) de meeste waarde voor geld. Driejaarlijkse KBO screening (vrouwen 40-49 jaar) in combinatie met mammografie (vrouwen 50-69 jaar) is daarna de meest (waarde-)renderende vroegtijdige opsporingsinterventie in Colombia.

Conclusies

In een poging om de hoge ziektelast van borstkanker in LMIL's te verminderen, worden er in dit proefschrift zorgvuldige aanbevelingen gedaan omtrent borstkankerbestrijdingsinterventies die in deze landen geïmplementeerd kunnen worden. De bevindingen van dit proefschrift laten zien dat screeningsinterventies door middel van klinisch borstonderzoek (KBO) kosteneffectief zijn (leeftijdsgroep 40-69) en voor de meeste LMIL's aan te bevelen zijn. Een belangrijk onderdeel van deze screeningsinterventies is het bewustmaken van borstkankersignalen en symptomen bij de te bereiken doelgroep. Om borstkanker vroegtijdig op te sporen, kan dit echter ook een economisch aantrekkelijke interventie op zichzelf zijn. Hoewel de extra investeringen voor het uitvoeren van deze vroegtijdige opsporingsinterventies aanzienlijk kunnen zijn, zijn de gezondheidsvoordelen voor de samenleving in het algemeen omvangrijker dan de extra kosten. Door deze interventies in LMIL's toe te passen, worden de beschikbare middelen in deze landen dus efficiënter ingezet.

Wanneer naast betaalbaarheid en kosteneffectiviteit, tegelijkertijd ook andere criteria worden meegenomen in het afwegingsproces, bevestigt dit proefschrift nogmaals dat screeningsinterventies door middel van KBO, in combinatie met de behandeling van borstkanker, prioriteit zouden moeten krijgen in LMIL's. Aromataseremmers kunnen eventueel ook worden ingezet bij borstkankerbehandelingen. Borstkankerscreening door middel van mammografie, het inzetten van taxanen of trastuzumab bij borstkankerbehandelingen, zou minder prioriteit moeten krijgen in LMIL's.

Desondanks zouden alle bouwstenen van borstkankerbestrijding (vroegtijdige opsporing, vroegtijdige diagnose, behandeling, follow-up en palliatieve zorg) voldoende beschikbaar moeten zijn in LMIL's, gezien al deze bouwstenen essentieel zijn voor het functioneren van borstkankerbestrijdingsprogramma's. Als de toegang tot één van deze bouwstenen ontoereikend is, of als adequate doorverwijzing tussen deze bouwstenen ontbreekt, zullen zowel de kwaliteit als de effectiviteit van het gehele borstkankerbestrijdingsprogramma afnemen.

Deze aanbevelingen stellen LMILs voor de uitdaging om al deze onmisbare bouwstenen te verbeteren en tegelijkertijd de essentiële borstkanker services toegankelijker te maken voor degenen die ze nodig hebben. Dit kost veel tijd en geld en vraagt dus bijzonder veel van LMIL's. Er lijkt dus een behoorlijke afstand te zijn tussen het doel om de duizenden vrouwen die ieder jaar weer sterven aan borstkanker te redden, en de realiteit van de beperkte mogelijkheden die er zijn in LMIL's. Het enige dat LMIL's kunnen doen, is om kleine stappen te nemen in de juiste richting en eerst prioriteit te geven aan betaalbare en integrale borstkankerinterventies zoals het bewustmaken van borstkankersignalen en symptomen, KBO screening, chirurgie, radiotherapie en eenvoudige palliatieve zorg. ***Life is not always a matter of holding good cards, but sometimes of playing a poor hand well***. De internationale gemeenschap zou onmiddellijk moeten beginnen met het ondersteunen van deze kleine stappen, omdat de toekomst van vele vrouwen en hun families in LMIL's afhangt van wat we vandaag de dag doen.

Acknowledgements | Dankwoord

Alles komt terecht.

We zijn er nog niet,

maar we zijn onderweg

(Huub van der Lubbe)

Het schrijven van het dankwoord van mijn proefschrift is een bijzonder moment. In 2010 ben ik begonnen met dit onderzoeksavontuur, een ontdekkingsreis naar onbekende oorden. Dit dankwoord betekent het einde van mijn avontuur. Ik heb nooit getwijfeld over deze ontdekkingsreis, omdat het mij kansen bood om aan de diepe behoefte naar het onbekende te voldoen. Bovendien ben ik er aan begonnen met de overtuiging om een positieve uitwerking op de bezochte landen te hebben op het gebied van borstkanker.

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List of publications

Peer-reviewd publications

- Sten G. Zelle, Rob Baltussen, Johannes D.M. Otten, Eveline A.M. Heijnsdijk, Guido van Schoor, Mireille J.M. Broeders. Predicting the stage shift as a result of breast cancer screening in low- and middle-income countries: a proof of concept. Journal of medical Screening. 2015 Mar;22(1):8-19.
- Kristie Venhorst, Sten G. Zelle, Noor Tromp, Jeremy A. Lauer. Multi criteria decision analysis for breast cancer control; the development of a policy tool. Cost Effectiveness and Resource Allocation 2014;12:13.
- Laurens M. Niëns, Sten G. Zelle, Cristina Gutierrez Delgado, Gustavo Rivera Peña, Blanca Rosa Hidalgo Balarezo, Erick Rodriguez Steller, Frans F.H. Rutten. Cost-Effectiveness of Breast Cancer Control Strategies in Central America: the cases of Costa Rica and Mexico. PLoS One. 2014 Apr 25;9(4):e95836.
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Other publications

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- Global Research Network on Urban Health Equity GRNUHE. Improving urban health equity through action on the social and environmental determinants of health. Final Report of the GRNUHE. July 2010.

Curriculum Vitae

Sten Gerrard Zelle was born on 28 March 1984 in Eibergen, the Netherlands. After completing his secondary school education at the Assink Lyceum in Haaksbergen, he started his studies at the Radboud University Nijmegen in the year 2002. During his Bachelor of Science in Biomedical Sciences he enrolled in a Minor Epidemiology. As a part of this minor he started a scientific research internship in 2006 in Jakarta, Indonesia, were he evaluated the survival of Indonesian prostate cancer patients.

Following this, Sten continued with a Master of Science in Health Technology Assessment with a strong emphasis on consultancy. Having developed an interest in international public health, he started an internship in 2009 at the Nijmegen International Center for Health Systems Research and Education (NICHE), which was part of the Department of Primary and Community Care of the Radboudumc. During this internship he worked for 8 months with the World Health Organization (WHO) at the WHO-CHOICE department in Geneva. He investigated the cost-effectiveness of breast cancer control interventions in Ghana and visited this country a number of times for field work.

In 2010, Sten enrolled in a PhD programme at NICHE, studying the cost-effectiveness of breast cancer control in different developing countries and working closely together with the WHO and the Erasmus University Rotterdam. This PhD programme led him to work in Ghana, Jordan, Peru, Colombia and India, where he coordinated scientific studies, held workshops, and performed site visits. During his PhD programme, Sten has been teaching in the International Public Health course at the Radboudumc and published in a variety of economical, clinical and health policy research areas.

Since 2013, Sten joined the Academic Collaborating Centre for Health in All Policies (AMPHI-IGB) as a postdoctoral researcher. There, he is responsible for the coordination and management of various community based research projects in the Nijmegen area.